VOLUME 19 NUMBER 5

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NOVEMBER, 1929

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 19 NOVEMBER, 1929 NUMBER 5

CORRELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION

I. GENERAL CONSIDERATIONS AND REVIEW OF THE LITERATURE *

G. DE TAKATS, M.D.†

CHICAGO

The relationship of the various structural elements of the pancreas has intrigued many investigators. Laguesse [1] evolved a remarkable theory of "balancement," maintaining that acini are continuously transforming into islands and that these two structures hold each other in a balance according to functional needs. A large series of experiments was conducted after the discovery of the islands to see what would happen to the islands when the external secretion was obstructed. The literature up to 1909 is summarized in Moldenhauer's inaugural dissertation;[2] the more recent studies have been discussed critically in Herxheimer's monograph.[3] One group of investigators firmly believes in a limiting membrane and a complete independence of the islands from the rest of the pancreas. A large number of investigators claim possible transitions of acini into insular epithelium. Another small but authoritative group of investigators concedes the proliferation and transformation of duct epithelium into islands when the duct no longer excretes.[4]

A study of the development of the islands led to the uniform result that the islands originate in small buds of the duct epithelium and can be recognized as early as in the embryo [5] of 80 mm. Here again, how-

* Submitted for publication, April 29, 1929.

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† Elizabeth Ward Fellow in Surgery.

1. Laguesse, F.: Preuves experimentales du balancement dans les ilots endocrinologics du pigeon, Compt. rend. Soc. de biol. **67**:94, 1909; Preuves experimentales du balancement dans les ilots endocrinologics du pancreas, J. de physiol. et de path. gén. **13**:1, 1911.

2. Moldenhauer, Johannes: Ueber das Verhalten des Pancreas, insbesondere der Langerhanschen Zellinseln nach Gangunterbindungen, Inaug. Diss., University of Bern, Wiesbaden, R. Bechtold & Company, 1909.

3. Herxheimer, G.: Pankreas, in Hirsch, M.: Handbuch der inneren Secretion, Leipzig, Curt Kabitzsch, 1927, vol. 1.

4. Otani, Sadao: Studies on the Islands of Langerhans in Human Pancreas, Am. J. Path. **3**:1 and 123, 1927.

5. Weichselbaum, S., and Kyrle: Ueber das Verhalten der Langerhans Inseln des menschlichen Pankreas im fötalen und postfötalen Leben, Arch. f. mikr. Anat. **74**:223, 1909.

S.H.W.

ever, some authors deny any relationship between glandular parenchyma and islands [6] whereas another group claims direct transitions from acini to islet tissue.[7]

The comparatively large amount of islet tissue in the fetal pancreas has been emphasized by two recent exhaustive studies of the embryology of the islands.[8] The maximal number occurs between the twenty-sixth and the thirty-second week. The number of islands then slowly diminishes up to birth, rapidly during the first postfetal year, and then again more slowly to the fourth year, after which their number remains fairly constant.

The observations on the pancreas of congenitally syphilitic children are interesting. The great increase in interstitial connective tissue prohibits the development of the glandular element, and a large number of small ducts and islands are visible. The appearance of the pancreas of a syphilitic new-born infant corresponds to a stage seen normally around from the seventeenth to the eighteenth week.[9]

The observations in pathologic processes of the pancreas, when a gradual obstruction of the external secretion has taken place, would indicate that not infrequently hypertrophy and hyperplasia of the islands occurred. In Koch's case [10] a marked increase of islands was found in spite of the fact that the entire gland had turned into an infiltrating scirrhus. That changes in sugar tolerance are frequently absent in carcinoma of the pancreas and chronic pancreatitis is generally admitted.[11]

In experimental ligation of the duct in the fetal pancreas in pancreatic cirrhosis and in carcinoma of the head of the pancreas there is one common feature: namely, the gland does not function as a gland of external secretion. The question arises whether or not the reversion of the gland to a stage of inner secretion alone might cause a preponderance of this part of the glandular function. Mansfeld [12] pointed

6. Nakamura, Nobu: Untersuchungen ueber das Pankreas bei Föten, Neugeborenen, Kindern und im Pubertätsalter, Virchows Arch. f. path. Anat. **253**:286, 1924.

7. Seyfarth, F.: Neue Beiträge zur Kenntnis der Langerhansschen Inseln im menschlichen Pankreas, Jena, Gustav Fischer, 1920.

8. Nakamura (footnote 6). Seyfarth (footnote 7).

9. Herxheimer (footnote 3). Seyfarth (footnote 7).

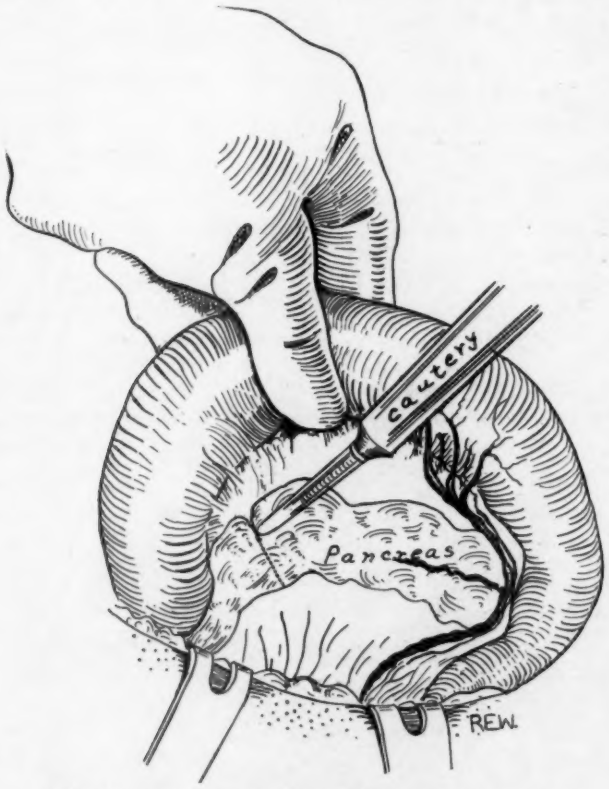
10. Koch, F.: Ein Adenom aus Inselzellen im Pankreas eines Nichtdiabetikers, Virchows Arch. f. path. Anat. **216**:25, 1914.

11. Gross, O., and Guleke, N.: Die Erkrankungen des Pankreas, Berlin, Julius Springer, 1924.

12. Mansfeld, G., and Szirtes, L.: Ueber die Beziehungen zwischen äusseren und inneren Secretion der Drüsen, Arch. f. exper. Path. u. Pharmakol. **130**:1 and 28, 1928.

out that possibly analogous conditions occur in the testis when the vas is ligated and in the parotid when Stenson's duct is tied. The thyroid gland possesses a duct at one time during development. The thyroid in the tunicates and in the amphioxus secretes a sticky material. In the higher vertebrates the internal secretion develops seemingly at the expense of the external secretion.

There is one condition that might possibly stimulate inner secretion of the pancreas, namely, the increased functional demand for such a



Division of the tail of the gland with electric cautery.

secretion. The islands do become larger in partially pancreatectomized animals,[13] and the pancreas of the diabetic person shows adequate proof of compensatory attempts.[9]

This study was undertaken for the purpose of examining the effect of isolation of the tail of the pancreas on its insular activity. While the external secretion could flow undisturbed into the duodenum, the tail would be converted into a ductless gland. Such a procedure was

13. Allen, F. M.: Glycosuria and Diabetes, Boston, W. M. Leonard, 1913.

suggested by Mansfeld,[14] who claimed an increase in sugar tolerance following such a procedure in the dog, lasting as long as three years. Alpern and Leites [15] confirmed his results in a short preliminary report. Nather, Priesel and Wagner,[16] who first confirmed Mansfeld's results, reported in a second paper that the increased tolerance is only temporary. Wohlgemuth [17] found a decreased sugar tolerance following ligations of the duct and believed it to be the result of a chronic sympatheticotonia with increased response to epinephrine.

This work was undertaken to study the histologic changes in the pancreas following the separation of the tail from the rest of the gland. In a second paper, the changes in sugar tolerance will be discussed, while other papers will deal with associated effects produced by partial pancreatic obstruction.

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14. Mansfeld, G.: Versuche zu einer chirurgischen Behandlung des Diabetes, Klin. Wchnschr. **3**:2378, 1924; Versuche zu einer operativen Behandlung des Diabetes, ibid. **6**:105, 1927; footnote 12.

15. Alpern, D., and Leites, S.: Ueber den Einfluss der Unterbindung des ductus pankreaticus auf den Blutzucker, Klin. Wchnschr. **4**:1551, 1925.

16. Nather, K.; Priesel, R., and Wagner, R.: Die Beeinflussung der Blutzuckerspiegels durch Unterbindung der Ausführungsgänge der Bauchspeicheldrüse beim Hund, Klin. Wchnschr. **5**:932, 1926; ibid. **6**:2089, 1927.

17. Wohlgemuth, Julius, and Mochizuki, N.: Ueber das Verhalten des Blutzuckers beim Kaninchen unter vorschiedenen Bedingungen und ueber seine Vertelung im Blut, Biochem. Ztschr. **150**:123, 1929. Wohlgemuth, J., and Seo, T.: Ueber experimentelle Erzeugung von chronischer Sympaticotonie beim Kaninchen, Biochem. Ztschr. **164**:271, 1925.

CORRELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION

II. THE HISTOLOGIC CHANGES IN THE ISOLATED TAIL OF THE PANCREAS *

G. DE TAKATS, M.D.†
CHICAGO

The purpose in this study was to examine the three main structural elements of the pancreas—acini, ducts and islands—after a part of this gland had been excluded from external secretion. It must be emphasized that this procedure is not identical with ligation of the duct, which method has been used to a great extent experimentally.[1] The exclusion of pancreatic juice from the intestines results in serious nutritional disturbances and may influence the inner secretion of the pancreas. Ligation of the tail of the pancreas, as suggested by Mansfeld,[2] leaves a sufficient part of the gland to secrete ferments and turns only ductless that part of the gland which is known to contain comparatively more islet tissue.

Recent studies by Ukai,[3] Herxheimer and Carpenter[4] and Jorns[5] uniformly state that a sclerosis of the pancreas takes place following ligation of the duct. The islands, however, resist this process, and may even increase in size. They even survive transplantation[6] for a long time. Special stains have been employed by some workers to identify the remaining structures as islet tissue.[7] A systematic examination of

* Submitted for publication, April 29, 1929.

† Elizabeth Ward Fellow in Surgery.

1. Moldenhauer, Johannes: Ueber das Verhalten des Pancreas, ins besondere der Langerhansschen Zellinseln nach Gangunterbindungen, Inaug. Diss., University of Bern, Wiesbaden, R. Bechtold & Company, 1909. Herxheimer, G.: Pankreas, in Hirsch, M.: Handbuch der innern Secretion, Leipzig, Curt Kabitzsch, 1927, vol. 1.

2. Mansfield, G., and Szirtes, L.: Ueber die Beziehungen zwischen äusseren und inneren Secretion der Drüsen, Arch. f. exper. Path. u. Pharmakol. **130**:1 and 28, 1928. Mansfeld, G.: Versuche zu einer chirurgischen Behandlung des Diabetes, Klin. Wchnschr. **3**: 2378, 1924; Versuche zu einer operativen Behandlung des Diabetes, ibid. **6**:105, 1927.

3. Ukai, L.: Morphologisch-biologische Pankreasstudien, Mitt. ü. allg. Pathol. u. path. Anat. **3**:1, 1927.

4. Herxheimer, G., and Carpenter, E.: Ueber das Verhalten der Langerhansschen Zellinseln des Pankreas und die Insulinbildung nach Gangunterbindung, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:270, 1927.

5. Jorns, G.: Die Sklerose des Pankreas nach Unterbindung des Ausführungsganges und die Transplantation des sclerotischen Gewebes, Beitr. z. klin. Chir. **139**:325, 1927.

6. Ukai (footnote 3). Jorns (footnote 5).

7. Kirkbride, M. B.: The Islands of Langerhans After Ligation of the Pancreatic Ducts, J. Exper. Med. **15**:101, 1913. Ukai (footnote 3).

the separated tail at various intervals to study the degenerative and regenerative processes of the pancreas was undertaken to serve as a basis for further studies.

METHOD OF EXPERIMENTATION

Healthy dogs weighing from 10 to 15 Kg. were used. The operation was performed with the animals under ether anesthesia after a preliminary injection of morphine, ¼ grain (16 mg.), and atropine, 1/60 grain (1 mg.). Through a small midline incision the index finger of the left hand palpated the pylorus and delivered the mobile duodenum into the wound. This brought the pancreas into the field. At the point where the tail of the pancreas borders the fixed part of the gland, a massive ligature was thrown around the gland. In later experiments the gland was cut between the two ligatures, or simply cut and the individual bleeders tied.[8] In the last six cases the gland was cut with the electric cautery.[8] This made the use of a ligature unnecessary. The absence of foreign material, thereby lessening the tissue reaction around the ligatures, was thought to be of some importance.

Sections were taken for histologic study at various intervals from the isolated and undisturbed portion of the gland. Ten of the twenty-five dogs used in this series lived a year or longer, whereas eighteen could be observed for at least six months. They were on the standard diet, and lost weight during the first few weeks, but maintained their weight later and seemed in good condition. Occasional blood counts revealed no kennel anemia. The removed specimens were fixed in a diluted solution of formaldehyde, U. S. P. (10:1) and stained with hematoxylin and eosin. Later, the neutral formol-Zenker fixation was used, and Bensley's special stains were employed.

SUMMARY OF HISTOLOGIC OBSERVATIONS

Two days following separation of the tail, the dominating impression was that of edema. The tail was soft and friable and was markedly swollen. The small ducts were dilated, and the acini were markedly distended with stagnant secretion. Their epithelium was flattened. The nuclei did not stain well, were irregular and had a hazy contour. The islands seemed swollen, but generally were intact (three specimens).

Two weeks following separation of the tail, the tail looked anemic and grayish white. Its consistency was hard and nodular, similar to that found in chronic pancreatitis of man. Under the microscope, the individual lobules were compressed and separated from each other by a moderate increase of connective tissue. This concentric, intralobular fibrosis caused the remaining parenchyma to stand out clearly. The acini still maintained their form, but the individual cells had partly undergone degeneration. The protoplasm consisted of numerous vacuoles; the nucleus was fragmented and pyknotic. The zymogen granules stained poorly. The small ducts were dilated; their epithelium showed infolding

8. Prof. W. T. Bovie and his staff of the department of biophysics have given their utmost cooperation. Dr. Bovie's newest model of high frequency apparatus was used (Surg. Gynec. Obst. **47**:751, 1928).

at certain places. There was marked mitotic activity. The islands seemed well preserved and showed no evidence of degeneration. In the sclerotic gland with compressed acini, they stood out clearly. There was no evidence of any activity on their part (three specimens) (fig. 2).

Four weeks following separation of the tail, the tail was even more sclerotic. It had turned into a whitish, narrow cord. Its consistency was hard and granular. There was more connective tissue than in the previous specimen, and not only interlobular but intralobular strands of fibrous tissue were seen. An increase in fatty tissue could also be observed. The acini were hardly recognizable, except as irregular masses

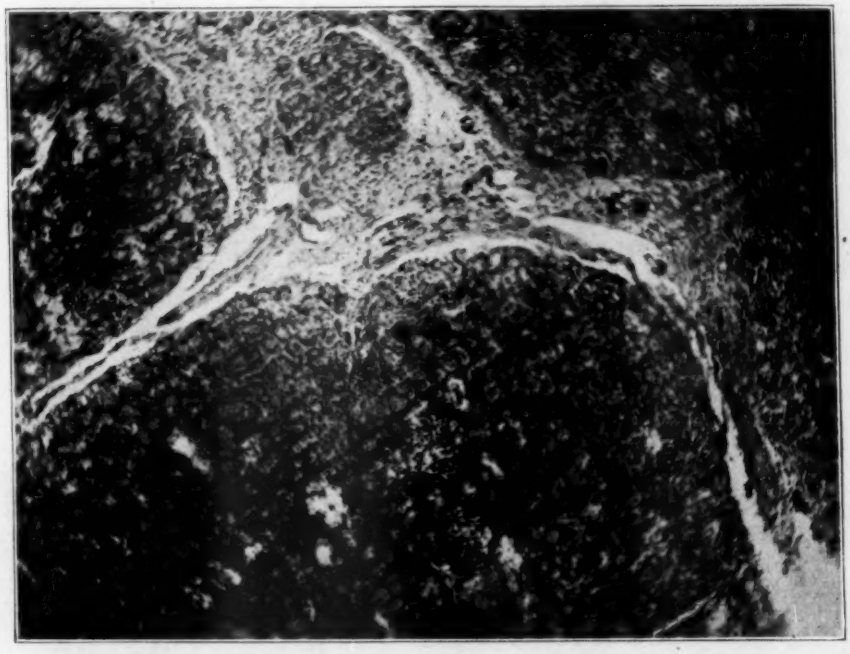

Fig. 1.—Two weeks following ligation of the tail. There is a moderate amount of perilobular sclerosis. The edema is most marked in the connective septums, but the islands are also swollen; low power.

of detritus into which connective tissue proliferated. The ducts were not dilated markedly; their wall was thick. Mitotic activity and occasional buds and infolding of the epithelium could be observed frequently. The islands did not seem increased in size or number. They stained well, but showed a certain diffuse hyaline-like structure in their center. There was no mitotic activity (two specimens) (fig. 2).

Six weeks following the separation, the tail was completely cirrhotic. Under the microscope, a dense connective tissue had taken the place of the lobules. Acinar structures could not be recognized. There was a marked proliferation of the minute ducts, which spread lengthwise and

crosswise over the field. Their epithelium was in a stage of mitotic activity. Occasionally, small buds, papillary folds and cystic dilatations could be found. The islands were still preserved, but were not particularly large or numerous except in one specimen, in which they stood out in large numbers. They did not show mitotic activity (three specimens) (figs. 3 and 4).

After twelve weeks, the microscopic appearance of the ligated tail was that of a whitish-gray firm cord. Histologically, the lobules had been compressed to small irregular structures. The connective tissue had proliferated into these lobules. The larger ducts were dilated, but

Fig. 2.—Four weeks following ligation. There is a marked increase of connective tissue, not only around but in the lobules. The acini are shrunken, and their cell nuclei are pyknotic. The islands are well preserved and fairly numerous; low power.

a few minute ducts were visible. The islands were numerous, and were not only well preserved, but larger in diameter. They showed mitotic activity. On one slide, in which the tail had been separated by the high frequency current, there was much less fibrosis, and the acinar structure was well preserved. The islands were numerous on the slide, and the number of capillaries around the islands was striking. This whole slide was characterized by a lack of fibrosis, but a large number of dilated capillaries was seen. The epithelium of the ducts was columnar with frequent mitoses and infolding. There was a mass of desquammated epithelium in the lumen (figs. 5 and 6).

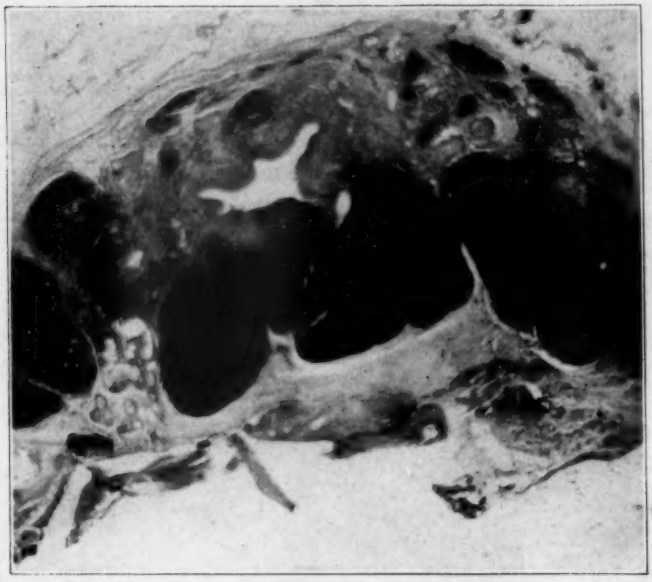

Fig. 3.—Isolated tail of the pancreas, six weeks following division with the cautery. The black areas represent glandular parenchyma staining red with acid fuchsin-methyl green stain. The fibrosis is fairly marked in the upper half of the section. The main duct is seen markedly dilated.

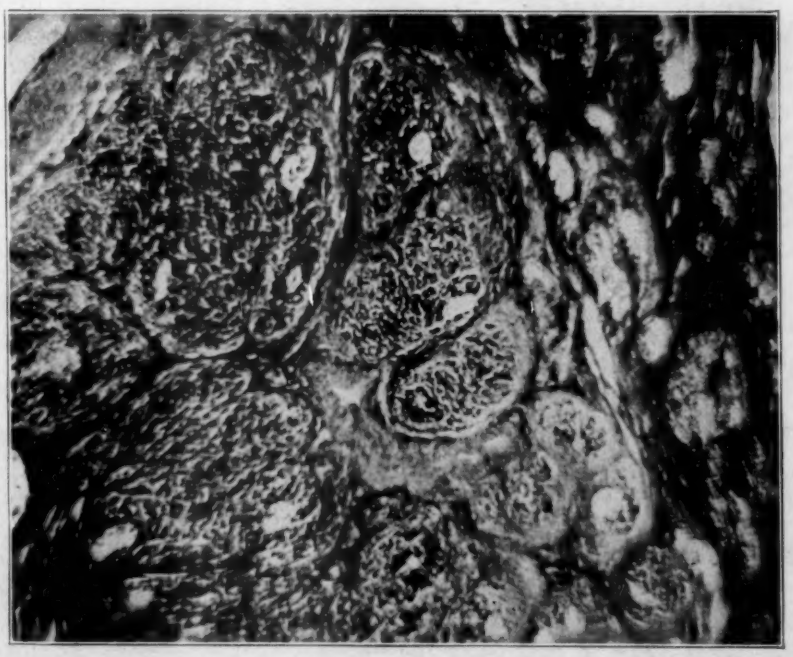

Fig. 4.—Same section as in figure 3, under high power. The lobuli are shrunken, and there is a great amount of connective tissue between the lobules. The islands are well preserved and are not involved in the sclerotic process.

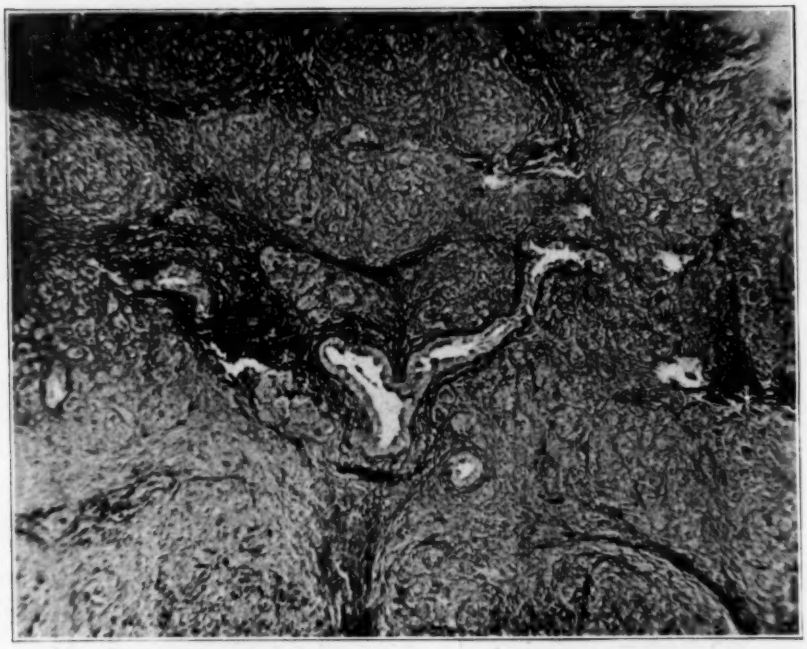

Fig. 5.—Twelve weeks following the isolation of the tail. There is a diffuse sclerosis of the gland. There are numerous small and minute ducts embedded in the sclerotic tissue. The epithelium of the ducts is high and shows infolding.

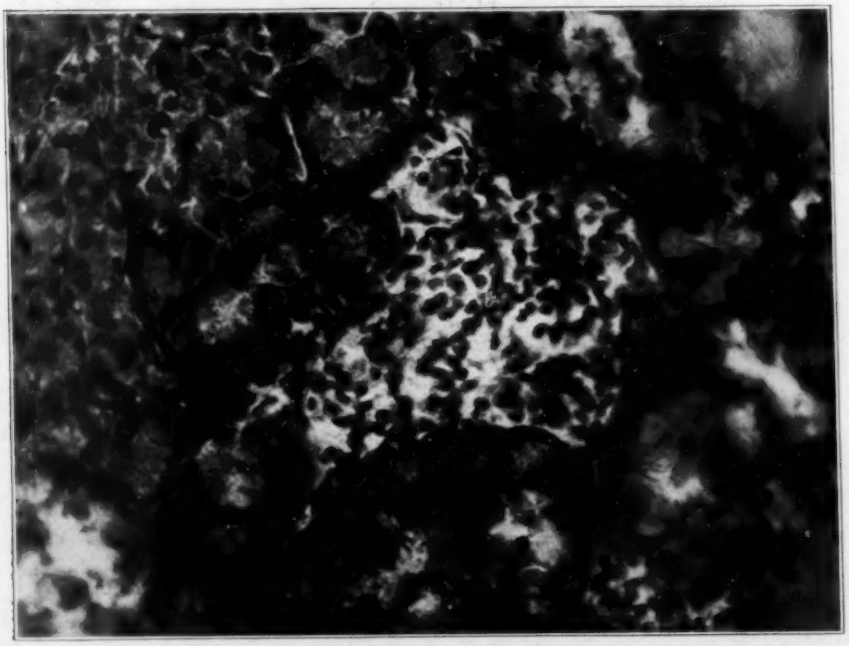

Fig. 6.—Same section as in figure 5, under high magnification, showing a well preserved island of considerable size. Below it is connected with another island which is probably the same island but hardly connected at the level of the section.

After sixteen weeks, the diffuse sclerosis with small remnants of acini dominated the field. The vessels had thick walls but were patent. The small ducts were numerous, and a large number of minute ducts was visible. Large masses of accumulated cells stood out in the connective tissue. Some of them were miliary abscesses. Others showed conglomerations of histiocytes and macrophages. There were epithelial cells with large light protoplasm which had the usual appearance of islet tissue. They were identified as such with special stains. These islets had a diameter of from three to thirty times the normal. In many

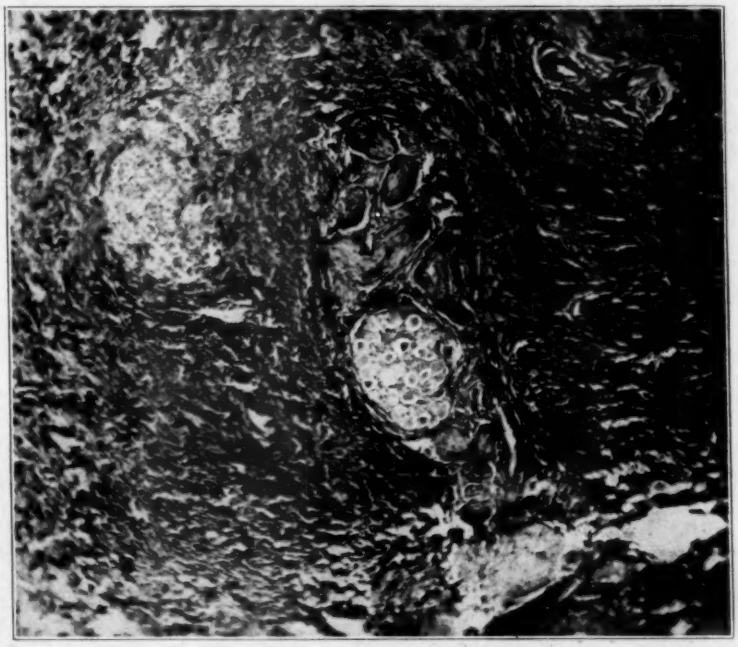

Fig. 7.—Sixteen weeks following ligation of the tail; there is complete absence of acini, and thickened but patent vessels. An intact ganglion is shown, and a large island appears in the left upper quadrant of the picture. There is no fibrosis within the island.

instances, they were grouped around a small duct with thickened walls (fig. 7).

After twenty-four weeks, no acinar elements could be detected in the sclerotic mass. Islet tissue was well preserved with typical capillary arrangement. The connective tissue was arranged in a wavy, circular configuration around the islands. In some places the solid epithelial masses seemed to be broken up by fibroblasts, and individual cells were visible. These nuclei seemed shrunken, and pyknotic (figs. 8 and 9). A transplant of a portion ligated twelve months previously had been made into the omentum. In the omental fat a large number of ducts

Fig. 8.—Twenty-four weeks following ligation; there are a number of small newly regenerated ducts, similar to the regeneration of bile ducts in cirrhosis of the liver. There are remnants of lobules seen in the periphery of the picture. There are small areas of round cell infiltrations, plasma cells and histiocytes as a result of minute focal necroses.

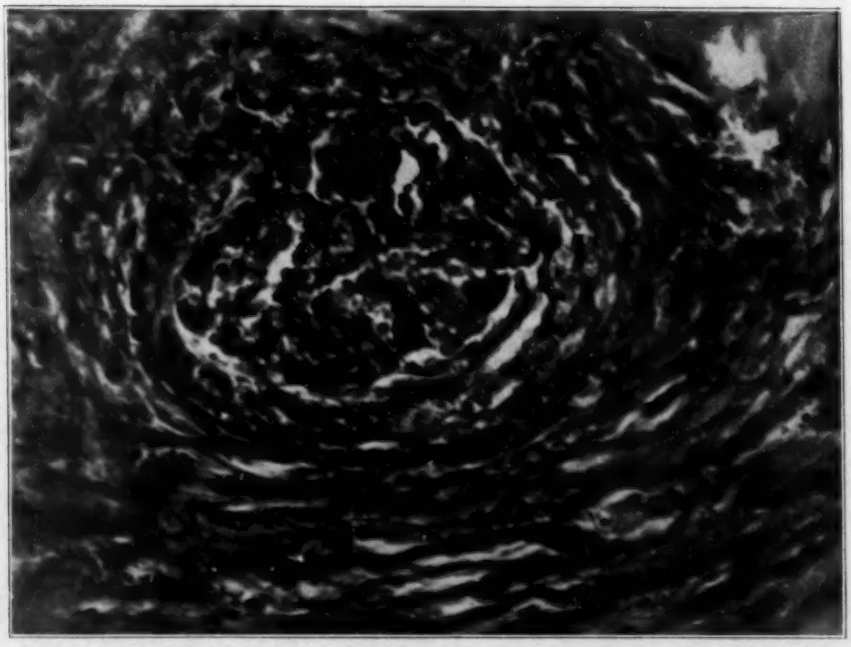

Fig. 9.—Twenty-four weeks following ligation. A large island, completely surrounded by insular waves of connective tissue, is seen. The island seems well preserved; the nuclei stain well.

with thick walls and high and frequently infolding epithelium were seen. Large structures of dendritic design, with light protoplasm and sharply staining nuclei were the only other cellular elements in the slides. These solid strands sometimes were drawn out to narrow cords. In other places, they formed round or oval structures with a lumen in the middle, as if they originated in ducts. Occasionally a small duct was found in the middle of these islands, with infolding epithelium. The transplant was well vascularized, a number of thick vessels surrounding the cellular elements in the omental fat. The sympathetic ganglions

Summary of Histologic Observations Following Isolation of the Tail of the Pancreas, with Four Additional Transplants into the Omentum

Postoperative Period, Days	Number of Specimens	Acini	Ducts	Islets	Ganglions	Connective Tissue
2	3	Distended	Dilated	Edematous	Edematous	General edema
14	3	Preserved	Epithelium active	Well preserved	Well preserved	Perilobular fibrosis
23	2	Poorly staining	Walls thick; infolding epithelium	Well preserved	Well preserved	Perilobular and intralobular fibrosis
42	3	Detritus	Desquamating epithelium	Numerous mitoses; well preserved	Well preserved	Dense fibrosis
84	3	No acinar structure	Dilated; few minute ducts	Numerous; large diameters	Well preserved	Very little fibrosis in the cauterized specimen
112	2	No acini plasma cells; histiocytes	Numerous minute ducts; buds	Large; mitoses	Well preserved	Very dense fibrosis
168	2	No acini	Ducts less numerous	Partly invaded by fibrosis	Well preserved	Intense sclerosis
210	2	No acini; fat	Occasional ducts	Well preserved	Well preserved	Intense sclerosis
360	1	Fat	Occasional ducts	Well preserved; vascular	Well preserved	Intense sclerosis
360 days; 160 days in omentum	4	Fat	Small ducts	Numerous	Well preserved	Intense sclerosis

were also well preserved. The number of ducts was markedly decreased in contrast with slides from transplants of less duration. When they were seen, their epithelium was active, showed a number of mitoses and was cuboid or cylindric (figs. 10 and 11).

Five such transplants remained in the omentum for six months or more. They all showed the same picture. The longest time was 450 days, the shortest, 150. Briefly, they were all characterized by a complete absence of zymogenic cells and by a dense fibrous tissue, in which only two elements survived—small ducts and solid masses of large cells—which stained like islets. The capillary arrangement around such masses was also similar, if not identical, to that around the normal islets. The diameter of these solid cell complexes was from ten to thirty times that of the islets in the dog. Other cell complexes of mesoblastic origin, as described in previous slides, were also encountered (see table).

Fig. 10.—Ligated tail of the pancreas grafted into omentum. The tail was separated one year before; it had been grafted in the omentum for three months. There is evidence of a good blood supply; a firm sclerotic mass was embedded in omental fat.

Fig. 11.—Same section as in figure 10, under high magnification. There are solid cell complexes surrounded by connective tissue, which may be identified with special stains as islands. Other groups of cells are seen, which consist of histiocytes and plasma cells, indicating the reaction of the omentum to the graft. No acini or ducts are seen.

OTHER OBSERVATIONS RELATING TO THE OPERATIVE PROCEDURE

The separation of the tail was first accomplished by throwing a wide tape around the body of the pancreas; also heavy linen ligatures and strips from the anterior rectus sheaths were used. When the abdomen was reopened at frequent intervals for obtaining histologic specimens, it was found that these ligatures would cause a marked inflammatory reaction with the outpouring of an exudate which in later laparotomies had organized into dense adhesions. In operations, when a ligature had been thrown around both head and tail for other purposes,[9] the right lobe of the liver was invariably sealed down to the duodenum and could be separated only with some difficulty. There was no evidence of fat necrosis, for which careful search was made. Fat necrosis, however, was encountered when extensive charring of the pancreas was produced with the electric cautery.

It was also found that in spite of the marked fibrosis and foreign body reaction that occurred around such ligatures a reestablishment of continuity between the body and tail was not impossible, as in two dogs the acinar structures were well preserved and the ducts undilated three months after the operation.[10] After this experience, the pancreas was doubly ligated and cut between two ligatures. The edema and exudation were just as marked as before, but I never encountered necrosis of the pancreas. As a matter of fact, it has been shown [11] that the pancreas may be simply severed and after ligation of the bleeding points be permitted to drain into the abdominal cavity without the appearance of necrosis in the pancreas.

The next modification was the use of Dr. Bovie's electric cautery. There was no need of ligatures either of the body or of the tail, and bleeders did not have to be tied. There was, however, a thin layer of desiccated tissue on either side of the cautery incision. At relaparotomy six weeks later, I found that the body and tail had been drawn together, and the original cautery incision could not be recognized without difficulty. This led me to interpose omentum between the two separated surfaces. This piece of omentum, which was wrapped around the separated tail, was examined histologically in six instances with regard to fat necrosis. In no case was it found.

The separation of the tail with the cautery, followed by wrapping it with omentum, was the technic finally adopted. In order to find out if the well vascularized omentum around the tail would hasten the absorption of cellular elements, free transplants of such tails that had been separated six months previously were made into the omentum and left

9. De Takats, G., and Nathanson, I. T.: The Effect of Ligation of the Tail of the Pancreas on Blood Diastase, Arch. Surg., this issue, p. 788.

10. The reestablishment of continuity is not undesirable, as it seems to lessen the degree of sclerosis. This question will be discussed in a later communication.

11. Crandall, L. A.: Personal communication to the author.

for three months. A section of such a transplant showed enormous islands with mitoses, all signs of sufficient circulation without any evidence that these structures were being absorbed. Ukai [3] saw islet tissue transplanted into the spleen after 450 days.

COMMENT

From the histologic studies it would appear that the separation of the tail of the pancreas from the rest of the gland results in a gradual disappearance of the acinar structures, replaced by fibrosis. There is no sudden necrosis "en masse" as would occur if the circulation was obstructed. It is possible, however, that circumscribed necrotic areas may result from acute or chronic pancreatic retention, as emphasized by Balo and Ballon.[12] The obstruction to the excretion of pancreatic juice must result in a greater intraductal pressure than the secretory pressure can overcome. The studies of Bensley [13] have particularly emphasized that duct epithelium soon starts to proliferate, becomes columnar and shows infolding. I have found this in my slides. The islands do not show any change at first aside from an initial edema, but from the sixth week on there is evidence of proliferation in the islet cells, and more new islands are seen. Whether these islands originate in the persisting islands, from scattered islet cells in acini, from acinar cells or from the proliferating duct cells, is not my purpose to study. All I can state is that I am confronted with large cell complexes, which show the vascular arrangements and staining properties of islet tissue. Such cell groups do not seem to degenerate, even if transplanted into omentum. The intensity of sclerosis is probably variable in different species; it is much less marked in the guinea-pig or in the rabbit.[14] A histologic study cannot give any information as to whether these cell complexes are functionally identical with islet tissue or whether their nervous control and physiologic response to stimuli are the same. Further work is necessary to study this question.

SUMMARY

1. The splenic portion of the pancreas was isolated from the rest of the gland in twenty-five dogs. The division with an electric cautery followed by wrapping omentum around the tail seemed the most satisfactory procedure.

2. Specimens were taken from the isolated tail at intervals of from two days to one year. After a short period of edema, a gradual destruction of the acinar elements takes place. There is an increasing amount

12. Balo, J., and Ballon, H. C.: Effects of Retention of Pancreatic Secretion, Surg. Gynec. Obst. **48**:1 (Jan.) 1929.

13. Bensley, R. R.: Studies on the Pancreas of the Guinea Pig, Am. J. Anat. **12**:297, 1911.

14. Bensley, R. R.: Personal communication to the author.

of connective tissue, first around and then within the lobules, and this finally results in pancreatic cirrhosis. The ducts are first dilated, then show proliferation and infolding of their epithelium; occasionally buds of epithelium form, resembling an early stage of embryonic development. A number of minute ducts also appear. The islands show edema for the first two weeks. Later there appear large solid cell complexes showing the vascular arrangement and staining properties of islet tissue. Fibroblasts may invade and break up the islets as the cirrhosis progresses.

3. Such an isolated tail does not tend to degenerate and undergo absorption for at least three months, if a free transplant of it is made into the omentum.

CORRELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION

III. THE EFFECT OF LIGATION OF THE TAIL OF THE PANCREAS ON DIASTASE IN THE BLOOD *

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AND
I. T. NATHANSON, B.S.
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In previous communications,[1] I have described the histologic effects produced by separating the tail of the pancreas from the rest of the body. It has been known since the work of Wohlgemuth,[2] confirmed by Noguchi [3] and by Gould and Carlson,[4] that the diastase in the blood rises for a short time following ligation of the duct. Our histologic studies have shown the presence of marked edema of the separated tail for the first two weeks, later followed by a gradual atrophy of the glands of external secretion. In this series of experiments we have attempted to correlate our morphologic observations with values for diastase in the blood.

The purpose of this study was to establish with a simple test whether ligation of the tail would cause an increased absorption of pancreatic diastase. It was undertaken to establish the duration of the pancreatitis following ligation of the tail. As clinical experience has repeatedly shown, acute pancreatitis will cause a marked rise in diastase in the blood. In ninety-seven cases of acute necrosis of the pancreas collected by Schmieden and Sebening,[5] seventy-eight cases (80 per cent) showed abnormally high figures. At the fifty-first German Surgical Congress,[6]

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* Submitted for publication, April 29, 1929.

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† Elizabeth Ward Fellow in Surgery.

1. De Takats, G.: Correlations of Internal and External Pancreatic Secretion: I. General Considerations and Review of the Literature, Arch. Surg., this issue, p. 771; Correlations of External and Internal Secretion: II. The Histologic Changes in the Isolated Tail of the Pancreas, ibid., p. 775.

2. Wohlgemuth, J.: Das Verhalten der Diastase im Blut, Biochem. Ztschr. **21**:381, 1909.

3. Noguchi, Y.: Ueber die Fermentdiagnose bei Pancreasverletzung, Arch. f. klin. Chir. **98**:545 (May 21) 1912.

4. Gould, C. K., and Carlson, A. J.: Further Studies on the Relation of the Pancreas to the Serum and Lymph Diastase, Am. J. Physiol. **29**:165, 1911.

5. Schmieden, V., and Sebening, W.: Chirurgie des Pancreas, Arch f. klin. Chir. **148**:319 (Oct. 27) 1927.

6. Discussion on paper of Schmieden, V., and Sebening, W.: Arch. f. klin. Chir. **148**:67 (Oct. 27) 1927.

Guleke, Unger and Heuss and von Redwitz emphasized the value of determinations for diastase in the blood or the urine. While it is recognized that determinations for lipase in the blood are a more sensitive index of pancreatic absorption,[7] the simplicity and ease with which diastase can be determined in the blood made this test preferable. It can be carried out in about forty minutes and is therefore useful in emergencies.

METHODS OF EXPERIMENTATION

Normal healthy dogs were used in the first control series. After the injection of morphine, ⅓ grain (0.02 Gm.), and atropine, 1/100 grain (0.001 Gm.), ether anesthesia was induced. The abdomen was opened with a short midline incision starting just below the xyphoid process. The duodenum was pulled forward two or three times. In other words, all the factors that are present outside of pancreatic ligation and that might have influenced our values were introduced. The duodenum was then replaced in the abdominal cavity. In a series of five dogs the values for diastase were taken every second day before, and a week after, the operation.

Determinations for diastase were made according to the original method of Wohlgemuth, as described by Unger and Heuss.[8] For the test the following materials were necessary:

2 cc. of blood serum (or urine)	2 pipets
1 per cent solution of sodium chloride	10 test tubes
1 per cent soluble starch	
Fiftieth-normal iodine solution	

About 10 cc. of blood is taken from the vein in a centrifuge tube, allowed to clot and separation of the serum permitted. One cubic centimeter of serum is pipetted into the first and second tubes. One cubic centimeter of 1 per cent solution of sodium chloride is pipetted into every tube. After the proper mixing of the serum and sodium chloride in tube 2, 1 cc. is again pipetted into tube 3. Here again after the proper mixing 1 cc. is pipetted over to tube 4, and so on up to the tenth tube, when the last cubic centimeter pipetted out of the tenth tube is discarded. To every tube 2 cc. of the soluble starch solution is then added, well mixed, and the whole system of tubes incubated in a thermostat at 38 C. for thirty minutes. At the end of that time, the fermentation is abruptly stopped by immersion of the tubes in cold water for a few minutes. Three drops of fiftieth-normal iodine solution are added to each tube. The undigested amylodextrin gives a blue reaction, the erythrodextrin, red and the achrodextrin, yellow. The end-point is read at the tube which shows the first trace of purple without being a solid blue. The quantity of ferment is calculated by raising the amount of starch (2 cc.) to the power which is indicated by the number of that test tube which is the last not to turn blue. For instance, if the end-point is at the fourth tube, $D = 2^4 = 16\ \frac{38^\circ}{30}$, indicating at the same time the temperature and duration of incubation. The Wohlgemuth unit, then, is the amount of diastase which will digest 1 cc. of 0.1 per cent of starch solution in thirty minutes at a temperature of

7. Grassberger, A.: Diastase und Lipase Werte im Blut bei operativ gesetzten Pankreasverletzungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:1, 1928.

8. Unger, E., and Heuss, H.: Zur Frühdiagnose der akuten Pankreasnekrose, Zentralbl. f. Chir. **53**:1500, 1926.

38 C. The diastasic values in the blood of the dog, $D = \frac{38}{24h}$, vary between 160 and 320.[8] Our normal figures taken in more than fifty individual determinations vary between 32 and 64, with an occasional reading of 96 following an incubation period of thirty minutes.

Following the exploratory laparotomy, determinations for diastase were made on the second, fourth, sixth, eighth and tenth days. We found that food, at least the food which the dogs are fed in the laboratory, does not influence values for diastase. Blood did not have to be taken then on the fasting animal.

In a second series of experiments, the tail of the pancreas was ligated as described in a previous communication,[9] and determinations for diastase were made every second day for two weeks.

In a third series of experiments, not only the tail but the head of the pancreas was ligated with a double silk ligature. Thus, only about the size of a quarter

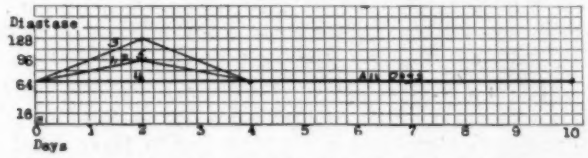

Chart 1.—Diastasic values in the blood following an exploratory laparotomy with the animal under ether anesthesia, with the preliminary medication of morphine and atropine. The duodenum was pulled forward and the pancreas lightly grasped. The maximum rise is 128, average rise, 96. Numbers 1, 2, 3, 4 and 5 indicate the five dogs used in this control series.

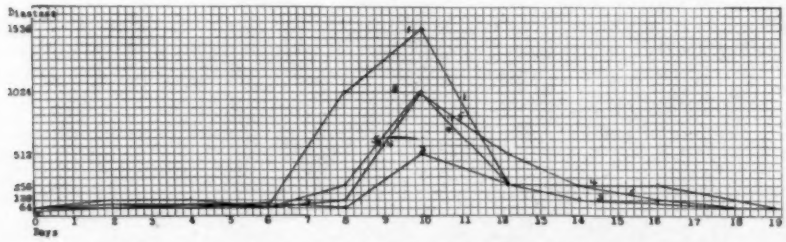

Chart 2.—Diastasic values in the blood following ligation of the tail of the pancreas. There is a small initial rise, comparable to that of the first chart in dogs used as controls, but more protracted, and a sharp secondary rise between the sixth and eighth days. The peak in this series is reached on the tenth day, after which there is a sharp drop.

remained around the main duct for the purposes of external secretion, while the rest of the gland was barred from secreting into the duodenum. Thus, a maximum amount of ferment absorption could be expected without the elimination entirely of the secretion into the duodenum.

RESULTS

Following an exploratory laparotomy with the animals under ether anesthesia, with preliminary medication of morphine and atropine, there

9. De Takats (footnote 1, second reference).

was no appreciable rise in diastase in the blood. The maximum rise on the second day was D $\frac{38°}{30} = 128$, the average rise, 96 (chart 1). The ligation or isolation of the tail of the pancreas resulted in a small but definite initial rise, followed by a second marked rise beginning between the sixth and eighth days. The diastase in the blood rose to 1,024 and 1,536 (chart 2). In a third series, in which both the head and the tail were ligated, sharp immediate rises were observed up to 3,072. About the tenth day, the values came down to normal and remained so (chart 3).

Chart 4 shows the average values of the three series of experiments on a total of fifteen dogs.

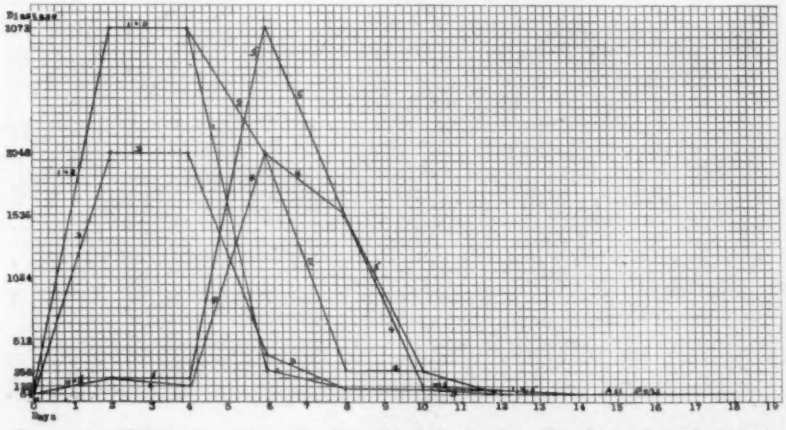

Chart 3.—Diastasic values in the blood following ligation of both head and tail of the pancreas. There is a sharp early rise, and a sudden drop on the tenth to twelfth days, after which the diastase does not rise.

COMMENT

Values for diastase in the blood of the normal dog seemed fairly constant and varied from 32 to 64 with the technic described. Food or an exploratory laparotomy did not influence these values to any extent. The ligation of the tail of the pancreas resulted in a small initial rise followed by a large secondary rise in the diastase in the blood. Such a secondary rise was described after ligation of the pancreatic duct by Gould and Carlson. They expressed the belief that the second rise occurred when the zymogenic cells recuperated from the edema which followed the operation. In our histologic studies, edema was the dominating picture observed immediately following ligation. As it subsides around the tenth day following operation, the coincidence of such histologic observations with the rise in diastase in the blood is striking. The amount of gland tied off at the operation seems to influence the diastasic values. In the third series, in which both the head and the tail

were ligated, the diastase rose to enormous values soon after operation. No secondary rise was noted, however, as if by that time there was no further excretion of diastase. At all events, this determination seems to be a sensitive index of acute pancreatic obstruction. That it gives only increased values in acute conditions has often been emphasized clinically. This is easily understood if we consider that the acini, the excreting ducts of which are obstructed, undergo degeneration as reported in our histologic study. The fact that the high diastasic values following glandular ligation return to normal within two weeks might be interpreted in a way that acinar elements in the ligated portion have ceased to excrete. This question is now under investigation with another method of approach. The formation of a pancreatic fistula from the

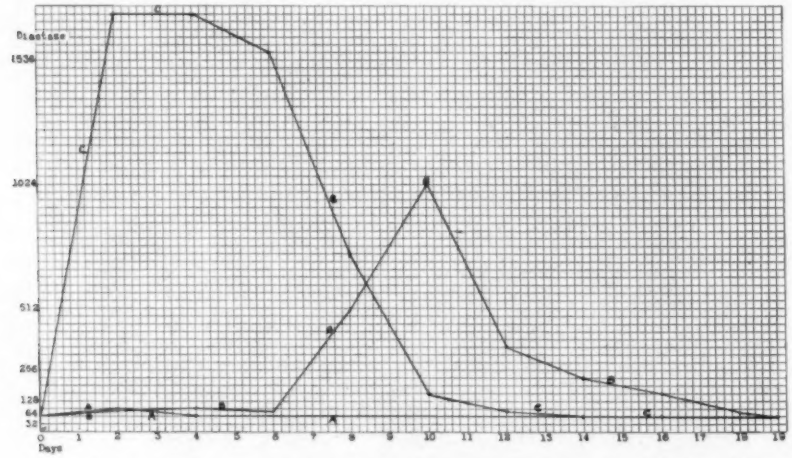

Chart 4.—Average curves of charts 1, 2 and 3. The small early rise following ligation of the tail is more protracted than in the control animals. The secondary rise in dogs with ligation of the tail shows its peak when the enormous rise following ligation of the head and tail has almost subsided (tenth day). *A* shows the average curve for the dogs used as controls; *B*, that for dogs on which ligation of the tail was done, and *C*, that for dogs on which ligation of both the head and the tail was done.

isolated tail is not probable, if the obstruction can be maintained for two weeks.

The original test of Wohlgemuth is simple and rapid and can be carried out without any special apparatus. We were especially interested in using such a test because of the possibility of a wider clinical use. We are aware that this method has been modified repeatedly and other methods described. Some insist on the use of buffer solutions in order to establish an optimal p_H for diastasic activity. A recent article of Elman and McCaughan [10] measured the lowering of the viscosity as

10. Elman, R., and McCaughan, J. M.: The Quantitative Determination of Blood Amylase with the Viscosimeter, Arch. Int. Med. **40**:58 (July) 1927.

effected by the starch-splitting ferment. While the importance of the buffers is clear in determinations of diastase in feces and urine, the buffer system of the blood is a reasonable safeguard that large variations in p_H will not occur. While the optimal p_H may not be thus obtained, the figures are comparable. The use of buffer solutions complicates the method without being of marked advantage. A few comparative determinations with the buffer method of Stafford and Addis [11] convinced us that buffering in the blood is not of any advantage. Our curves showing the amount of diastase following ligation of the tail or the head and tail show that a definite and constant rise is estimable.

We have no experience with the interesting method of Elman and McCaughan, as our work was completed at the publication of their method. These authors made the statement that diastase in plasma deteriorates rapidly, whereas diastase in serum retains its potency. We have used diastase in serum all through our work and have kept serums in the icebox for two days without deterioration. Checks on the p_H of serum have shown no change in the serums which would warrant buffering.

Another advantage of determining diastase in the blood instead of in the urine is the factor of concentration and the rate of excretion of urine, as has been emphasized by Stafford and Addis. Determinations of diastase with feces introduce additional difficulties, as recently discussed by Wolfer and Christian.[12] The clinical application of a simple determination of diastase in the blood in suspected pancreatic injuries and in acute necrosis of the pancreas is well worth considering. No increase can be expected in chronic pancreatitis and obstruction.

SUMMARY

1. Isolation or ligation of the tail of the pancreas leads to an early increase in diastase in the blood, followed by a secondary rise about the seventh day. From our previous histologic studies, we believe that the secondary rise may be due to the disappearance of the initial edema.

2. The rise in diastase seems to be proportionate to the amount of tissue ligated. The ligation of both the head and the tail of the pancreas gave much higher rises in diastase than ligation of the tail alone.

3. The return of the diastasic values to normal at the end of two weeks would indicate that external secretion is not to be expected or feared from the ligated portion after two weeks.

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11. Stafford, D. D., and Addis, T.: Diastase Determinations in Urine and Blood as a Method for the Measurement of the Functional Capacity of the Kidney, Quart. J. Med. **17**:151, 1924.

12. Wolfer, J. A., and Christian, L. W.: Pancreatic Function Tests, Arch. Surg. **17**:899 (Dec.) 1928.

EXPERIMENTAL SARCOMA OF BONE*

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It is known that an experimental tumor on transplantation invariably reproduces the same kind of tumor as to cell type. For instance, the Rous sarcoma always produces a fibrosarcoma whether it is injected into muscle, bone, connective tissue or an internal organ, such as the liver. When, therefore, an opportunity came to work with an endothelioma, I seized the chance to observe its behavior when injected into the bone-marrow of chickens. The purpose of such a procedure was several fold. First, it was desired to see to what extent it might produce a tumor resembling the much disputed tumor described by Ewing as an endothelioma of bone. Second, it seemed important to watch the development of tumor of the bone-marrow from its inception, a thing impossible to do in man, since in the latter it usually has advanced considerably before it is discovered. Third, the reaction of the bone itself to the presence of cells of known origin might throw some light on the type of cell that is capable of forming bone.

This tumor was found by J. A. Murray, director of the Imperial Cancer Research Fund, London, in a Rhode Island Red chicken. It was furnished me through the courtesy of Dr. W. E. Gye. The material received had been dried in London three weeks before it was used. It was said by Murray that filtrates of the tumor, as well as suspensions of the cells, would reproduce the tumor on injection into an homologous strain of chickens. The new tumors therefore presumably arise from cells of the new hosts, and not from the transplants.

Murray, in a communication through Dr. Gye, said that by serial sections he had observed the tumor arising from the lining cells of blood vessels. My first experiment was an attempt to prove this. Suspensions of the tumor cells were injected into the thigh muscles of chicks, and the animals were killed at various intervals in order to watch the development of the resulting tumors. Into half the chicks, a small amount of ground carbon was injected with the tumor cells in order that the sites of the inoculated material might be localized. The tumors grew, as a rule, rapidly. Within thirty-six hours, microscopic nodules were present between the muscles. When carbon also was present, growth was even

* Submitted for publication, March 22, 1929.

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* Part of this work was done in the Department of Pathology, Harvard Medical School. The x-ray pictures were made at the Peter Bent Brigham Hospital, Boston, under the direction of Dr. M. S. Sosman.

more rapid. Carbon alone, injected into several control chicks, or into the opposite thighs of the chicks receiving tumor cells, caused a proliferation of the same kind of cells as those which formed the tumor. This proliferation never became malignant, but remained as a typical foreign body reaction. Both the tumor cells and the cells responding to the injection of carbon alone were phagocytic. Many of them became filled with the carbon (fig. 3).

Because of the rapidity of growth and the intimate intermingling of tumor cells, blood vessels and connective tissue, it was not possible to say,

Fig. 1.—An early stage of the tumor, starting in the muscles of the thigh. The cells appear to be growing from the sarcolemma, and are forming sinuses; × 80.

beyond the shadow of a doubt, from which cells the tumors arose. In muscle, the first cells to appear seemed to come from resting cells between the muscle or the connective tissue fibers, or perhaps from the mesothelium forming the surface cells of the sarcolemma. These cells were undifferentiated and contained considerable lightly staining cytoplasm and round or oval nuclei with prominent nucleoli. They resembled the reticular cells of man more closely than the endothelial type of cells. The former have a reticulated chromatin, the threads of which commonly join at a concentrically placed nucleolus; in the latter, the chromatin is

in finely scattered granules, among which nucleoli can often not be distinguished. The cells of the tumor in the chicken thus resembled the cells lining lymph sinuses, and were comparable to the Dorothy Reed cells of the Hodgkin's type of lymphosarcoma. They formed spaces and lined them (fig. 1), and some of the spaces contained blood. Mostly, however, the tumor grew in lobulated masses, and had a capillary stroma, except where thin bands of fibrous tissue divided up the tissue.

In bone-marrow, the tumor cells appeared to arise from the indifferent cells lining the marrow sinuses, and appeared first as spindle cells without fibrillae. Here, again, it was impossible to say from which type

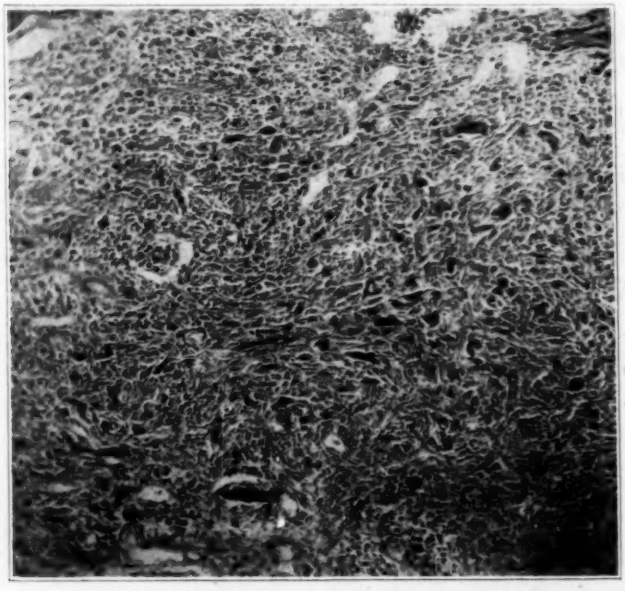

Fig. 2.—A proliferation of cells in the bone-marrow four days after the injection. Carbon is present. There was no evidence of tumor in the x-ray picture; × 80.

of cells the tumor cells arose. There seemed to be a general reticular hyperplasia, and the cell which became a tumor cell could not be distinguished from a similar (or identical) cell which formed the blood cells. Carbon pigment stimulated the proliferation of the same kind of cell here also.

In transplantations of the tumor cells into the bone-marrow, young chicks from 3 to 10 weeks old were used. It was comparatively easy to inject the ground-up tumor suspended in salt solution into the marrow cavity of the tibia through the proximal articular surface. The animals were killed from time to time, some as early as twenty-four hours after the inoculation. X-ray pictures were made from the first day, until it

was found that tumors could not be demonstrated before about the fourteenth day. Sixty-five chickens were used, and practically all developed tumors. The results, in those which were allowed to run the full course, were about the same. Therefore, to be brief, only a few cases will be given in detail.

At twenty-four hours, no tumor could be observed microscopically. Tumor cells which had been injected could be identified in some cases, and these were undergoing autolysis. On the second and third days following the injection, a reaction on the part of the marrow could be observed as a proliferation of undifferentiated cells. These cells appeared

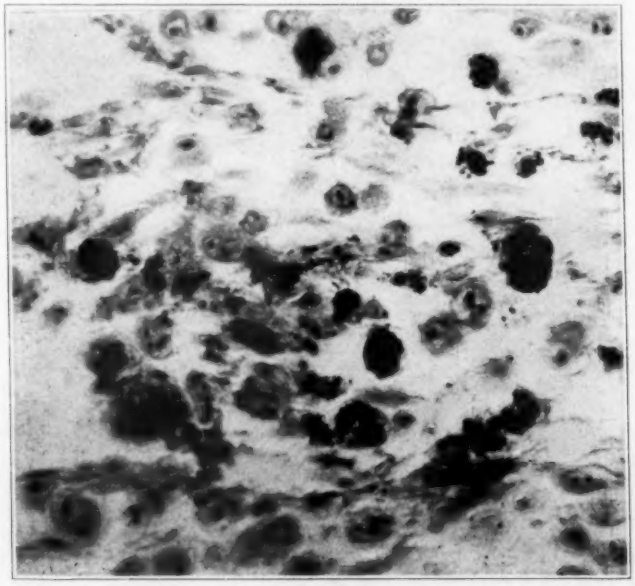

Fig. 3.—A higher magnification of the cells four days after the inoculation with the tumor. Their phagocytic character is shown; × 480.

no different from those which presumably were forming white blood cells, and at this time a definite diagnosis of tumor could not be made. In those cases in which carbon had been injected, the cells were phagocytosing the pigment. Definite tumor could be diagnosed on the fourth day in four chicks by microscopic examination (fig. 4). The cells at this stage were of spindle shape, but staining with phosphotungstic acid hematoxylin failed to demonstrate fibroglia.

At later stages, the tumor grew up and down the medullary cavity, though in most cases the tumor reached the outside before entirely replacing the bone-marrow. Tumor could not be demonstrated by palpation or by the x-rays in any chick before the fourteenth day. Of ten

chicks that were allowed to live beyond this period, one contained a palpable tumor on the fourteenth day, three on the fifteenth, two on the sixteenth and two on the eighteenth. The x-rays revealed tumors in one chick on the fourteenth day, in two on the fifteenth and in one on the sixteenth. These were animals which had been followed systematically by taking daily pictures. Two such chicks died before palpable tumors appeared, one on the fifteenth day and one on the nineteenth day. Each of these contained metastases in the liver and the spleen, and gross tumor was present in the tibia (on longitudinal sectioning),

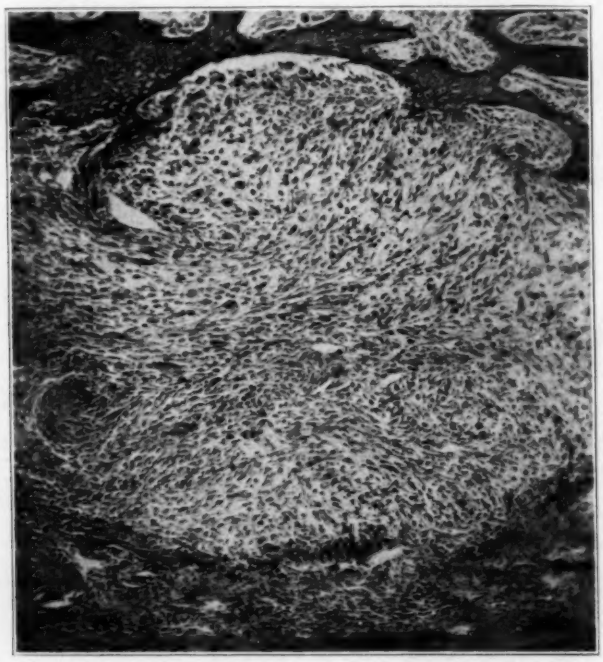

Fig. 4.—The picture shows the size of the tumor of the bone-marrow at four days. No carbon was injected. No tumor was shown by the x-rays; × 80.

but tumor could not be diagnosed from postmortem x-ray pictures. All the chicks that were allowed to die of tumor succumbed before the twenty-second day following the injection. The clinical course of one chicken is given as an example of the usual progress of the tumor.

Chicken 36.—A suspension of cells from a large tumor of the thigh was injected into the left tibia of chick 36 when it was about 2 months old. X-ray pictures were made daily, beginning on the sixth day, until the death of the chicken, on the eighteenth day. The tumor became visible on the sixteenth day (fig. 5*A*); a slight roughening of the periosteum was shown, with a suggestion of fine, radiating lines. On the seventeenth day (fig. 5*B*), both sides of the shaft showed rarefaction and had a mottled, ragged appearance, and radiating lines

and an elevated periosteum were present on one side. Fig. 5 *C* shows the tumor on the eighteenth day, when a definite fusiform thickening of about a third of the shaft could be detected.

At autopsy, huge metastases were found in the liver and metastases also in the lungs and the spleen. The tibia contained tumor throughout the marrow cavity, and this had broken through in the region of the nutrient artery to form a subperiosteal mass which completely encircled the cortex. Between the periosteum and the cortex there was a new formation of bone. In the medullary portion, the tumor was soft and gray and contained numerous small areas of necrosis (figs. 6 and 7 show a more advanced tumor of similar appearance). Histologically, the tumor consisted of the type cells, previously described, in a capillary stroma. These cells seemed to be differentiating into the cells that were forming bone beneath the periosteum.

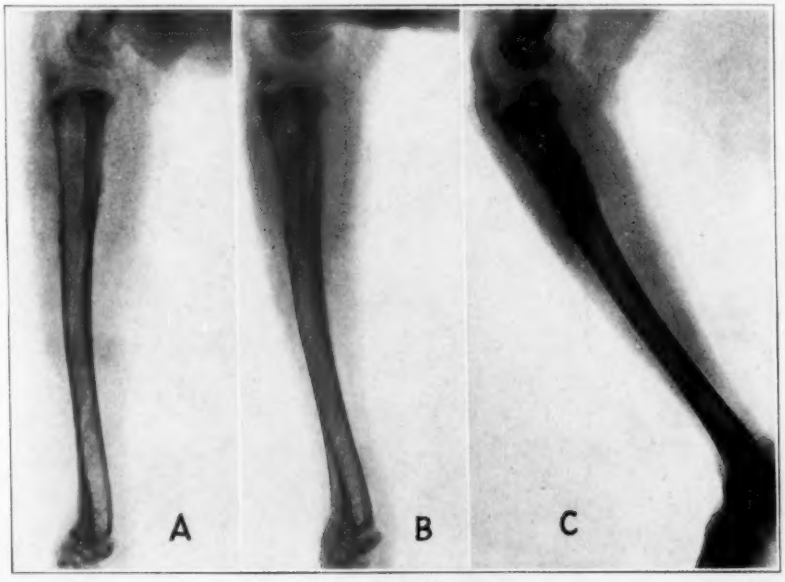

Fig. 5 (chick 36).—*A*, the first definite evidence of tumor shown by the x-rays, on the sixteenth day; *B*, the tumor on the seventeenth day, showing rapid growth; *C*, the tumor on the eighteenth day, on which the chicken died. The x-ray picture is of the detached leg.

A single experiment was undertaken with the Rous fibrosarcoma for purposes of comparison with the endothelial tumor. A cell suspension received from Dr. J. H. Mueller of the Department of Bacteriology, Harvard Medical School, was injected into two barred Plymouth Rock chickens. The site of injection was, as in the case of the endothelial tumor, the tibia. One animal was killed on the sixteenth day. A definite tumor was present, which was passing out into the subperiosteal space around the nutrient artery (fig. 8). The second chicken was killed on the twenty-first day. A fusiform tumor was found similar to

that formed by the endothelioma. The cells of the tumor were apparently forming the bone that was present in considerable amount between the periosteum and the cortex.

The endothelial tumor was not an exact reproduction of the endothelial myeloma of Ewing. It had characters both of Ewing's tumor

Fig. 6.—A tumor that caused death in twenty-one days with generalized metastases. The medulla is filled with tumor, the cortex is eroded and masses of tumor and new bone are present between the periosteum and the cortex; × 4.

and of osteogenic sarcoma. The type cell, as has been said, was different, though the cells of chickens do, in general, differ from the cells of man in several respects. The tumor grossly resembled Ewing's tumor in that it fairly well filled the marrow cavity, it occupied more than a third, sometimes nearly all, of the shaft, and it had osteolytic rather

Fig. 7.—The tumor forms bone only when confined beneath the periosteum. At one place in this section, where the periosteum has broken down, no bone is formed; × 4. Figure 11 shows the x-ray picture of this bone.

than sclerosing properties while confined to the medulla and the cortex. It was pointed out previously [1] that any tumor of bone (metastatic or primary) may cause the formation of radiating spicules as seen by the x-rays. This, however, is much more common in osteogenic sarcoma than in other tumors, and is one of the least conspicuous features in Ewing's tumor. The method of growth of this experimental tumor beneath the periosteum exactly duplicated a subperiosteal osteogenic sarcoma as seen in man. Such tumors were previously called periosteal sarcomas, until Codman [2] pointed out that all of them are both medullary and subperiosteal, and claimed that all arose in the medulla. The

Fig. 8.—Rous sarcoma. This shows one way by which the tumor passes out of the medullary cavity: the cells infiltrate along the nutrient artery and form a subperiosteal tumor; × 80.

tumors in the chickens illustrated admirably two ways by which a medullary tumor reaches the subperiosteal region: one by way of the nutrient foramen, and another by growing between bone spicules and along the haversian systems (figs. 8 and 9).

So far as the second purpose is concerned, that is, the following of a tumor of bone from its inception to its termination, there may be

1. Connor, C. L.: Endothelial Myeloma, Ewing, Arch. Surg. **12**:789 (April) 1926.

2. Codman, E. A.: The Nomenclature Used by the Registry of Bone Sarcoma, Am. J. Roentgenol. **13**:105, 1925.

differences of opinion as to how far one may go in comparing a tumor in the chicken to one in man. Generally, in man, a tumor has been present for a considerable period before attention is called to it by some untoward occurrence, but usually there is no means of ascertaining how long. The factor of pain, of course, was not evident in the tumors in the chickens, if present. Most of the chicks showed no signs of distress until metastases were far advanced. Two only limped, and each of these had developed small nodules on the articular cartilage at the site of injection. Pain, as a rule, is the symptom that draws attention to a tumor of bone in man, although cases are not infrequent in which a spontaneous

Fig. 9.—Another way in which a subperiosteal tumor is formed: the cells of an endothelioma infiltrate through bone trabeculae and pass along beneath the periosteum; × 80.

fracture is the first sign. One cannot compare the two growths, therefore, in this respect. One may only record that, in the chickens, fully two thirds of the course of the tumors had been run before they were detectable, in spite of the fact that first signs were eagerly awaited.

There has been discussion regarding the nature and causes of the new formation of bone in both primary and metastatic tumors of bone. It is fairly well agreed that the formation of new bone around a metastatic carcinoma or a giant cell tumor is a reparative, reactive or defensive process, similar to the fibrosis occurring around tumors in soft tissues.

But it is conceded that osteogenic tumors form tumor bone, and many older pathologists professed to distinguish between bone formed by tumor cells and that formed by normal osteoblasts. Many osteogenic tumors form abortive or malformed bone, but many also form bone that is indistinguishable from that seen in a normal callus. Eising,[3] on philosophical evidence, believed that the bone formed in all tumors is reactive, and not formed by tumor cells. It seems reasonable, however, that osteoblasts in an osteogenic tumor might form an osseous tissue just as fibroblasts in a fibrosarcoma may, and do, form collagen.

Fig. 10.—Formation of bone, apparently by tumor cells, between the periosteum and the cortex; × 80.

Granting, then, that tumor cells may form bone, from what cell or cells may osteoblasts be derived? In most cases, these undoubtedly arise from spindle cells (fibroblasts?) of the periosteum and endosteum. The latter, however, is in man a rather indefinite membrane, and in young animals osteoblasts may apparently be derived from the marrow.[4]

3. Eising, E. H.: Bone Formation in Osteogenic Sarcoma: Teleologic Considerations, Arch. Surg. **12**:867 (April) 1926.

4. Keibel and Mall: Human Embryology, Philadelphia, J. B. Lippincott Company, 1910, vol. 1, p. 303.

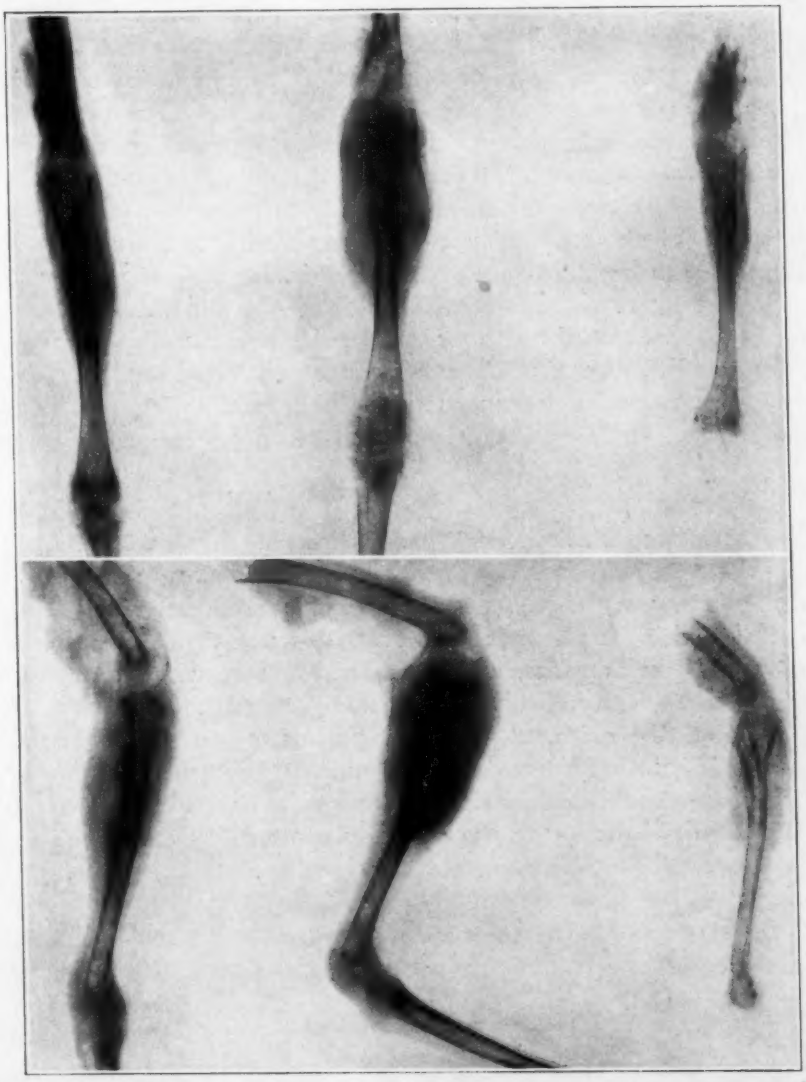

Fig. 11.—Three stages of growths in chicks of the same age, all at twenty-one days.

Moschcowitz,[5] discussing heterotopic formation of bone, declared that the osteoblast comes from an endothelial cell lining blood vessels, and further stated that a common cell (fibroblast?) forms the endothelial cell, the osteoblast and the bone-marrow cell. Maximow [6] derived the histiocyte, the fibroblast and the reticular cell from a common mesenchymal cell, and the osteoblast from the fibroblast. Fibrils, similar to those of a fibroblast, may be formed by the monocyte in tissue cultures.[7]

In the present experiments, two types of tumors, a fibrosarcoma (Rous) and an endothelioma (or reticuloma), produced bone under one condition only, namely, when the cells were confined between the periosteum and the cortex. There are probably three reasons for this: (1) both types of cells are capable under certain conditions of forming osteoblasts; (2) the conditions are probably a suitable physicochemical milieu, such as is found in the region of bone, and (3) a mechanical restraint similar to that caused by tumor growing between a tautly drawn periosteum and the cortex of bone. Once the periosteum has been broken through, the tumors grow much more rapidly, and no intercellular substance of any kind is produced by the endothelioma.

SUMMARY

A spontaneous transmissible endothelioma of the chicken was introduced into the marrow cavity of the tibia of the chicken for the purpose of duplicating, if possible, a tumor similar to that described by Ewing as an endothelial myeloma, and in order to watch the development and manner of growth of such a tumor. The resultant tumor resembled, in some respects, both endothelioma and osteogenic sarcoma as seen in man. Like endothelioma, it occupied a large part of the shaft and was osteolytic until it had penetrated via the nutrient foramen or through the cortical spicules to the subperiosteal space. While confined between the periosteum and the cortex, the tumor cells formed radiating spicules of bone. In a similar experiment with the Rous fibrosarcoma, it, too, formed bone beneath the periosteum.

Fully two thirds of the course of the tumor had been run before the tumor became palpable or visible by the x-rays, although it was

5. Moschcowitz, E.: The Relation of Angiogenesis to Ossification, Bull. Johns Hopkins Hosp. **27**:71, 1916.

6. Maximow, A. A.: Relation of Blood Cells to Connective Tissue and Endothelium, Physiol. Rev. **4**:533, 1924.

7. Fischer, A.: Sur la transformation in vitro des gros leucocytes mononucléaires en fibroblasts, Compt. rend. Soc. de biol. **92**:109, 1925. Carrel, A., and Ebeling, A. H.: Pure Cultures of Large Mononuclear Leucocytes, J. Exper. Med. **36**:365, 1922. Maximow, A. A.: Development of Nongranular Leucocytes (Lymphocytes and Monocytes) into Polyblasts (Macrophages) and Fibroblasts in Vitro, Proc. Soc. Exper. Biol. & Med. **24**:570, 1927.

present in all the bones examined on the fourth day. By the twenty-second day, the chickens had died with widespread metastases. Two died of metastases before a tumor could be demonstrated by palpation or by the x-rays, although tumors were present in both cases.

It is shown that both endothelial (or reticular) cells and fibroblasts are capable of differentiating into osteoblasts under certain physical and chemical conditions.

PULMONARY ATELECTASIS AND RESPIRATORY FAILURE *

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NEW YORK

In an earlier publication, I [1] described the abrupt onset of respiratory embarrassment in cases of caseous pneumonic phthisis complicated by sudden atelectasis. Observation of a large number of severe and extensive cases of acute phthisis has convinced me that this complication is not the exception, but rather the rule, in such severe processes of the lungs. To illustrate the extent to which such conditions may progress, a case is here presented which is only one of many such observations. This particular case was chosen because it shows atelectasis of an entire lung which cleared up ultimately, in spite of catastrophic progress of the process itself. Furthermore, since this patient died of a miliary dissemination shortly afterward, an opportunity was afforded to check up on the pathologic changes.

The patient, J. G., aged 25, a bank clerk, became ill suddenly about six weeks previous to his admission, in the first days of January, 1925. His first roentgen examination is not reproduced here, as it was not much different from the plate given here with the date of March 4, 1925. The patient was too ill for any active therapy to be attempted. On April 9, 1925, he developed symptoms of acute respiratory distress. The plate of that date (fig. 2) reveals as the reason for the attack a massive atelectasis of the entire left side of the lung. Figure 3, taken on May 15, 1925, shows reinflation of the formerly collapsed lung, except for some extension of the process into the lower lobe, as compared with the first plate. The patient died two months later. Autopsy revealed vast honeycombing throughout the left lung, with cavities of different sizes and shapes. The intervening pulmonary tissue was studded with tubercles. The pleura of the left side was densely adherent. The right lung showed lobular involvement in the upper lobe and miliary dissemination throughout the rest of the lung.

Here, then, was a case in which spread of an acute exudative process from the upper to the lower lobe was accompanied by a temporary collapse of the entire lung. Atelectasis and retraction of severely affected lungs in the course of phthisis has been described in the literature repeatedly; recently Packard [2] reported such cases. More or less atelectatic collapse of severe tuberculous lesions has been observed to be a regular feature of phthisis. That atelectasis is also a regular

* Submitted for publication, April 29, 1929.

1. Rappaport, I.: Am. Rev. Tuberc. **18**:447, 1928.
2. Packard, E. H.: Am. Rev. Tuberc. **18**:7, 1928.

feature of other severe pulmonary diseases has become increasingly evident within the last decade. Churchill and Holmes [3] reported atelectasis in pulmonary suppuration of pyogenic etiology. The Philadelphia workers on atelectasis conclusively demonstrated its presence in all postoperative complications of the lungs. Coryllos and Birnbaum [4] recently presented experimental evidences to prove that atelectasis is the underlying pathologic change of all pneumonic processes.

In short, there is ample clinical and pathologic evidence to the fact that pulmonary processes of whatever etiology are accompanied by atelectasis of greater or lesser areas of the lungs. The clinical symptoms

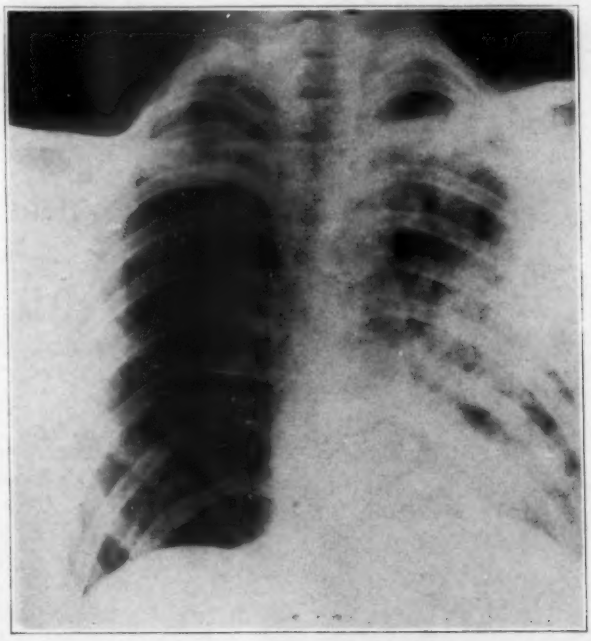

Fig. 1.—Lungs of the patient, J. G., taken on March 4, 1925.

of atelectasis are identical, regardless of the underlying pulmonary disease. The symptoms of critical pneumonia, massive collapse or any other critical condition of the lungs are exactly the same; they are those I have described under the name of "anoxemic cardiac syndrome." They are the symptoms of acute respiratory embarrassment, which vary in intensity according to the proportion of breathing surface failing

3. Churchill, E. D., and Holmes, G. W.: Lobar Atelectasis in Chronic Pulmonary Suppuration, Arch. Surg. **14**:1093 (May) 1927.

4. Coryllos, P. S., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung: Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929.

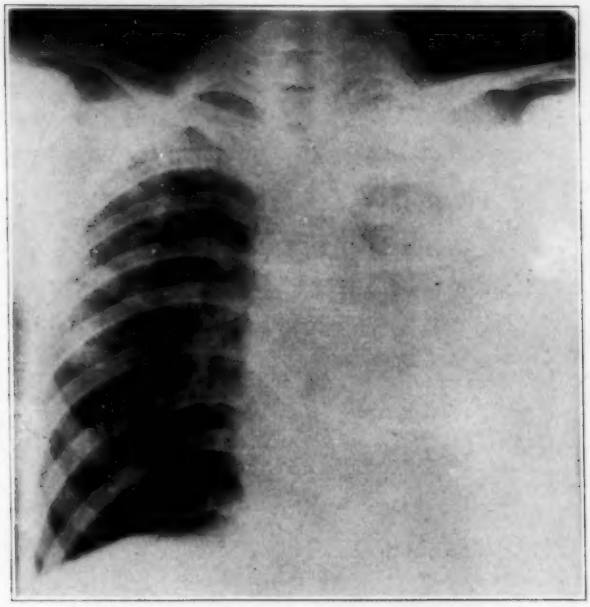

Fig. 2.—Lungs of the patient, J. G., taken on April 9, 1925, showing a massive atelectasis of the entire left side of the lung.

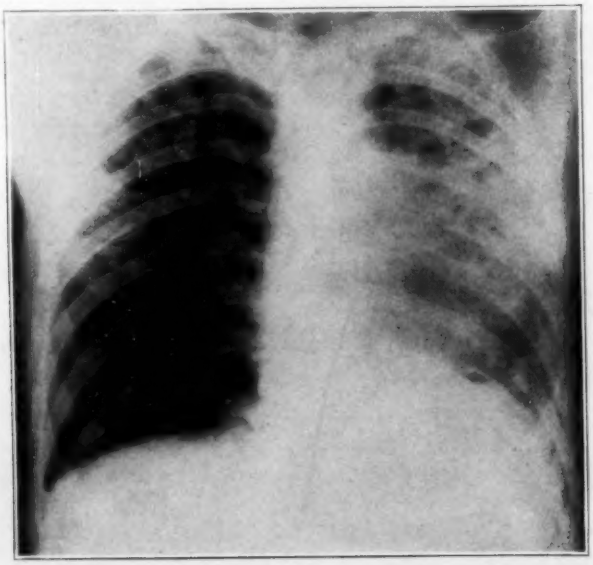

Fig. 3.—Lungs of the patient, J. G., taken on May 15, 1925, showing reinflation of the formerly collapsed lung except for some extension of the process into the lower lobe.

in function, and according to the compensatory capacity of the breathing surface remaining in function. In the aforementioned paper on the respiratory failure syndrome, I have described its acute form and emphasized that it shows a wide range of variations according to the degree of respiratory dysfunction present. As a basis for the discussion in that paper, I adopted the present day pathologic concept that respiratory embarrassment leads to failure by way of cardiac exhaustion and that the clinical phenomena are therefore cardiac in origin. However, even at the time that the paper was published I believed in a different conception of respiratory failure, but I was not yet ready to bring out the subject in the light of my own conceptions.

The recent studies, experimental as well as clinical, with the revival of the discussion of pulmonary atelectasis in the literature, afford me the opportunity to attempt the presentation of my own conceptions. My studies of respiratory failure date back to the last twelve years of clinical observation of a great number of respiratory failures in such wartime mass affections of the lungs as epidemics of influenza, pneumonia and gassing. These clinical observations have convinced me that respiratory failure is never associated with cardiac failure, and that chronic respiratory failure leads only to a relative circulatory insufficiency, but not to cardiac failure. My clinical observations have brought me to the conclusion that pulmonary atelectasis is the pathologic substrate of the clinical entity of respiratory failure. Pulmonary atelectasis and respiratory failure are the two sides of the selfsame clinicopathologic process. Respiratory failure, of whatever etiology—suffocation, infection or obstruction—always appears with atelectasis as the pathologic, and the "respiratory failure syndrome" as the clinical, accompaniment of the disease.

An attempt will be made to present this conception and the physiologic, pathologic, experimental and clinical data supporting it.

In these days of functional medicine it is not customary to propose changes of theoretical conceptions without offering some new and personally produced experimental evidences. I have no such evidence, as mine is purely clinical. Disease is nature's great biologic experiment that unrolls itself before the eyes of the clinician. The respiratory conditions here discussed are of a purely functional nature and run their course like true experiments. The old problem of pulmonary collapse has now been revived, owing to the fact that x-rays have demonstrated it to be the center of events in almost every form of pathologic process of the lungs. Besides the problem of collapse of the lungs, respiratory pathology is riddled with unsolved problems, such as asthma, emphysema, edema of the lungs, etc. It is in the nature of respiratory function—alveolar respiration and pulmonary circulation—that these processes are so deeply hidden from observation, and even from the

possibility of satisfactory experimental investigation, and their integration must apparently remain forever largely a matter of intuition. Physiology and pathology offer one nothing but working theories. Why should the clinician not be permitted to offer his conclusions and working theories, based on his clinical experiences?

This venture in expounding my own evolved conceptions about these respiratory problems offers the only excuse, that it merely proposes to replace old assumptions by new ones. The only difference, as it appears to me, is that while the old assumptions raise new questions and run counter to one's clinical experiences, these new assumptions answer many questions and are congruent with the established clinical facts.

To present a problem of such dimensions in as brief a form as I intend to give here, I shall have to restrict myself to the mere outline of the ideas and the facts supporting them. Let them speak for themselves.

Every pulmonary disease, regardless of its etiology, presents the caleidoscopy of decompensation and failure in some parts of the lungs with compensation of the other parts. My first task must be, therefore, to define the pathologic and clinical phenomena of decompensation and failure as well as those of compensation in pulmonary function. For this purpose I must go back to the basic conceptions of the physiologic and pathologic processes of respiratory function, after which I shall deal with the clinical features.

PHYSIOLOGIC CONSIDERATIONS

According to the up-to-date conceptions of respiratory function, breathing depends on the following mechanism. Inspiration is carried out by the activity of the external respiratory muscles under voluntary nervous control; expiration depends on the activity of the intrinsic muscles of the bronchi under vegetative nervous control. There is a prodigiously overprovided huge area of breathing surface, which undergoes little movement, but which is served by the supple systems of air and blood channels, so constructed that they can adapt themselves to a wide range of changes in respiratory requirements. Both the bronchi and the pulmonary arteries are endowed with the same elastic and smooth muscle structures, enabling them to undergo tremendous changes of capacity. According to the proportion of breathing surface in function and the intensity of this function, the wide range of variations in the capacity of the air and the blood passages is brought into play. These changes are precisely coordinated; they are always simultaneous and proportionate. With each inspiration both bronchi and arteries equally increase their capacity to receive the simultaneous increase of air and flow of blood brought to the lungs. The funda-

mental mechanism underlying normal respiratory function is this respirocirculatory correlation. Blood arrives in the lungs with a pressure so low that its circulation through the lesser circuit is maintained almost exclusively by the force of the pulmonary function of the respiratory excursions. Thus, air and blood in the lungs are promoted by the selfsame mechanism, the respiratory movements. It is a basic principle of pulmonary function that in any unit of the lungs there can be no circulation without ventilation, and that there can be no ventilation without circulation. With few limitations one can carry this principle still further and say that hyperventilation of a pulmonary unit means also its hypercirculation, while hypocirculation means also its hypoventilation. It is this precise correlation between ventilation and circulation that underlies the mechanism set in action with all variations in respiratory requirements. In exercise, increase of respiratory volume is parallel with increase in circulatory volume, while in sleep the opposite occurs. One must assume that this correlation is as precise in each unit of the lungs as it is in the whole of it. This correlation inherent in pulmonary function regulates the relation between pulmonary air and the blood depot from the first to the last breath. With the first breath of the infant, and closure of the botallian duct, a definitely correlated air and blood depot is established in the lungs, which is to be maintained to the last breath. The lungs, as the heart, never rest, and are never empty of blood or air. They are kept in constant expansion, under Donders' pressure, by the permanent presence of the air and the blood depot, which must ever be balanced to one another if function is to be maintained intact. Hence, there results the arrangement of residual air and blood volumes in the lungs, the air and blood depot, which are being constantly refreshed by the arrangement of tidal volumes of air and blood. The constant exchange of the pulmonary air and the blood depot is carried out by the same mechanism, the respiratory excursions, that coordinates the respirocirculatory correlation.

PATHOLOGIC CONSIDERATIONS

From the standpoint of functional pathology the most outstanding feature of respiratory function is the phenomenon of simultaneous compensation and decompensation present in the different parts of the same lung, or in the two lungs. Unlike the heart—an organ, all parts of which must stand or fail together—the lungs are a conglomeration of organ units, with a remarkable degree of functional independence. The units of the lungs behave independently and exactly like the whole of the lungs; they can fail separately, and can compensate one for the other. This situation permits a generalized discussion of respiratory failure, speaking from a purely functional standpoint. Whether decompensa-

tion or failure is local, restricted to a greater or lesser area of the lungs, or whether it is general, affecting the whole of the lungs, the pathologic sequence of events is the same. It will always depend on the interrelation of the failing and compensating areas of the lungs, of a restricted or general character.

As I have said, the foundation of normal respiratory function is the precise respirocirculatory correlation. This correlation is most precise when pulmonary function is kept at a mean standard. Diversions from the mean in respiration are fraught with upset in the correlation. Such an upset is equivalent to disturbed respiratory function, which may lead to respiratory decompensation or even failure. Accordingly, both extremes of hypofunction and hyperfunction are likely to lead to respiratory decompensation by way of upsetting the correlation between air and blood depot. Owing to this peculiar situation, one has the unusual opportunity in respiratory function, a phenomenon without its likeness in any other organic function, to be able to bring about respiratory decompensation at one's will. One can observe transitions from normal function to respiratory decompensation in normal persons by voluntary apnea and exhaustion from excessive exercise.

In voluntary apnea—Valsalva experiment—one sees phenomena threatening collapse of the lungs, if the experiment is carried too far. A depletion of the air depot and a marked increase of pulmonary blood depot, excessive pulmonary plethora, result. In lack of ventilation, transmission of blood through the lesser circuit drops far below the simultaneous reduction of blood supply. Even the reduced amounts of blood brought to the lungs under these circumstances are sufficient to bring about an excessive pulmonary plethora as compared with the reduced air depot, or state of pulmonary expansion. Hypofunction of any part of the lungs under a certain level produces such a local plethora, causing an engorgement. Patients with adequate circulation when immobilized in bed, so that expansion of pulmonary areas is markedly reduced, always develop such congestions. Any form of defective breathing, smothering or obstructed breathing is productive of such plethora. Hyporespiration, carried to the point of complete standstill for more than a few minutes, brings about such proportions of pulmonary plethora that alveolar capillaries become engorged. This also immobilizes the alveoli and interferes with their function, with the result that blood flow is still further reduced. Extreme engorgement of the alveolar capillaries follows, which changes the permeability of the tissues, permitting the transudation of blood serum into the tissues and air spaces. Atelectasis of the involved area of the lungs is thus produced. This is exactly what happens in complete occlusion of a bronchus, or the complete occlusion of the trachea.

The same result is produced in a somewhat different manner in hyperfunction that may be so excessive as to lead to pulmonary failure. The sequence of events is best illustrated in exhaustion from exercise, which is, paradoxically as that may sound, a physiologic form of respiratory decompensation. In excessive exercise the trained person has the ability of maintaining a precise correlation of excessively increased air and blood depot; not so, however, the untrained person. Such persons soon reach the limit of their ventilatory capacity, the greatest air and blood depot they can manage, beyond which they lose their power of correlation. In such persons, air and blood depot increased beyond a certain point become unmanageable, and the pulmonary emphysema and plethora, of a compensatory nature, become stagnant, because exchange must slow down. The reason for this slacking down of the turnover is, the slowing down prolongation of expiration, or expiratory dyspnea. It is a significant fact, that it is always expiration—depending on the activity of the intrinsic bronchial muscles under the control of the vegetative nervous system—that fails in respiratory function exceeding a certain level. The excessive pulmonary plethora and obstructive, stagnant emphysema thus produced are the phenomena of so-called respiratory decompensation. Carried beyond this point, hyperrespiration leads only to the further increase of pulmonary plethora, and finally to such capillary engorgement that pulmonary rigidity results. Capillary engorgement causes interference with alveolar function, and is the pathologic substrate of the clinical phenomenon one calls dyspnea. Pulmonary rigidity closes a vicious circle by which the lungs are completely immobilized; the circulation of the blood is severely handicapped, and the serum will leak into the tissues and air passages. Thus is pulmonary atelectasis produced by hyperfunction carried beyond a certain point.

Of course, normally the excessive dyspnea will stop men from carrying pulmonary plethora to the point of failure. However, instances of such fatalities in athletics that are carried to excess are described in the literature frequently. In excessive exercise, already at the point of considerable pulmonary plethora, people begin to cough and expectorate. Especially in dogs is the hacking and the emission of copious secretions from the lungs conspicuous. As a matter of fact, every pulmonary disease produces pulmonary plethora, hence the most outstanding feature of cough and expectoration in all of them.

The aforementioned mechanism by which respiratory failure arises in a quasi physiologic manner is also the mechanism by which it is produced in all pulmonary diseases, regardless of their particular pathogenesis. Hence, pulmonary atelectasis is of so variable a pathogenesis. Any disease of the lungs, whether its cause is mechanical, infectious or nervous, etc., leads to functional disturbance of greater

or smaller parts of the lungs and produces decompensation in some areas and compensation in other areas. The greater the failing area and the more severe it is, the greater must be the area of compensation or the more intense its hyperfunction. A struggle for predominance develops, on the outcome of which the final issue depends. The tendency will be on the part of the compensating area to help eliminate the failing part from function altogether. This is achieved by the "shunting" away of its blood supply and hastening its atelectasis and collapse by expanding at its expense. There are two good reasons for this tendency. First, if the blood supply of such an area of excessive plethora is maintained, and if the transudation of such large amounts of serum into the air spaces is kept up, the whole lung is threatened with overfilling. Such a condition was described by C. Jackson,[5] who called it, "the drowning of the patient in his own secretions." Second, the compensatory areas of the lungs, by their hyperexpansion and hypercirculation, will encroach on the space and draw on the blood supply of the immobilized parts of the lungs.

This situation leads to the most interesting clinical and roentgen phenomenon of paradox excursions of the failing or decompensating areas of the lungs, as compared with those in hyperfunction. In massive collapse of one lung, as well as in obstructive emphysema—bronchial obstruction—in one lung, one sees the involved side expand in expiration, and retract in inspiration. The reason for this is that in inspiration the hyperfunctioning side expands at the expense of the involved side and "shunts" away its blood supply. In expiration, the involved side increases in volume and receives blood which is squeezed out again in the next inspiration. This explains the transmission of considerable volumes of blood through atelectatic lungs, and is responsible for the anoxemia produced under such circumstances.

The struggle for supremacy is conspicuous and clearcut only when decompensation and failure are on one side and compensation on the other side. When both failure and compensation are scattered over the whole of both lungs, the phenomena are more complex but essentially the same. The result is also the same.

In the clinical discussion one will see that this is really the underlying clinicopathologic phenomenon of all pulmonary diseases. Here one may conclude that failure in function of a lung area results in the production of excessive pulmonary plethora which finally floods the air passages and produces atelectasis. In short, the functional pathologic substrate of respiratory failure is pulmonary atelectasis. It amounts to stoppage of the circulation within the affected area, with the result that local edema is produced.

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5. Jackson, C.: Laryngoscope **21**:1183, 1911.

That this must be true for the whole of the lungs as it is for its parts follows from the well established principle that the whole of the lungs behave exactly as the parts do. The manner in which a local respiratory failure isolated to a part of the lungs can involve the whole of the lungs and produce general respiratory failure is obvious from the foregoing descriptions. Failure of one part must be compensated by hyperfunction in another part. If the failing area is comparatively small or failure is mild, compensation soon gains the upper hand and all is well. But, if the area failing is large, or if failure is intense, compensatory hyperfunction is likely to become so excessive that its advantages are exceeded by its grave dangers. If the area of compensation is limited, or if its hyperfunction is extremely intense, it will either "shunt" away too large blood volumes or bring about excessive hypercirculation, and will be fraught with an excess of pulmonary plethora. Excessive pulmonary plethora will, of course, lead to decompensation of the hyperfunctioning areas themselves.

One sees this happen frequently in all pulmonary diseases that reach critical stages. It is a common observation in massive collapse, obstructive emphysema or pneumonia, that the hyperfunctioning side is frequently more resilient in expiration than in inspiration. The reason for these phenomena is that under these circumstances excessive pulmonary plethora is produced in the hyperfunctioning side, which is actually a handicap to its efficient compensation. The fatal consequences of this situation are conspicuous in critical cases of pneumonia. Here the exaggerated compensatory effort gets the functioning areas of the lungs into serious trouble. Excessive plethora is produced of such proportions that the air passages of the uninvolved lungs are flooded. When the rattling in the good lung is first heard in critical stages of pneumonia it is the surest sign of approaching catastrophe, for it is the sign of oncoming general atelectasis and pulmonary edema. Thus pulmonary edema—diffuse pulmonary atelectasis—becomes the pathologic substrate of general respiratory failure. Lack of space does not permit me to go into a detailed discussion of the great pathologic puzzle of pulmonary edema. However, I want to call attention to the following two outstanding facts of experimental pathology. Producing a wide opening of the chest, or thoracotomy, is the surest way to bring about pulmonary edema in an animal; yet wide opening of the chest is also the surest way of saving an animal and of stopping pulmonary edema produced by injections of epinephrine. This paradoxic puzzle of experimental pathology on which endless experimentation has been done and on which the most copious literature has been written is explained in the light of my conceptions in a most obvious manner.

To open the chest of an animal widely means the crudest interference with its respiratory mechanism; the respirocirculatory correla-

tion is upset; the lungs will collapse; transmission of the blood depot is severely handicapped, the final outcome of which is excessive plethora and pulmonary edema. In the animal in which pulmonary edema has been produced by injections of epinephrine, or for that matter any pulmonary edema, tremendous pulmonary plethora is already present, and is being combated by compensatory emphysema of a degree which the animal is still capable of raising. In pulmonary edema the struggle between emphysema and atelectasis is extremely acute, because it is widely diffused over both lungs, and emphysematous expansion is greatly handicapped. If under these circumstances the chest is opened widely, that is, if thoracotomy is performed, emphysema gains room for its expansion, and can combat atelectasis successfully.

In pneumonia, asthma, emphysema and other conditions of the respiratory tract, pulmonary edema is the cause of death because there is no room for emphysema to effect the necessary compensation. In all these conditions, pulmonary edema is caused directly by respiratory failure. I believe I have presented sufficient evidence to show that pulmonary edema is the pathologic substrate of respiratory failure.

PATHOLOGIC ANATOMIC CONSIDERATIONS

The pathologic anatomic phase of the question of pulmonary atelectasis is at present in considerable confusion. This is due mainly to the fact that the interpretation of the term "atelectasis" is generally too rigid. There is fairly general agreement as to the application of the term to conditions in which actual shrinkage, or collapse, of lung volume is coupled with simple edema. This rigid interpretation of the term has somewhat relaxed with the recent progress in the recognition of atelectatic conditions. The term has recently been extended to include processes showing infectious or collateral edemas. Until lately, Coryllos and Birnbaum [4] have advocated the application of the term to frank pneumonic processes.

Now the term "atelectasis" means lack of distention. There could be no more correct term for the condition. As has been shown in all pulmonary diseases, regardless of the etiology, immobility of the area of the lungs involved is the sole and paramount factor in the production of the changes. If one does not hold too rigidly to the restricted interpretation of atelectasis, the term will include every form of pathologic process of the lungs from collapse with simple edema, through all degrees of shrinkage of the pulmonary volume with transudation or exudation to infectious, collateral edemas and to pneumonia in which, though the volume of the lungs is augmented, airlessness and immobilization are complete. All of these conditions are based essentially on the same pathologic phenomenon, showing only different degrees of intensity. The outstanding features of all are: relative immobility to complete

fixation, lack of air to complete airlessness, emigration of blood elements into the air passages to their complete overfilling with these elements. All these conditions are forms of atelectasis of different quantitative degrees. The forms of atelectasis as found at autopsy show a wide range of variations as to the volume of the atelectatic lung and as to the morphologic elements which make up its histologic structure. The particular features of the different diseases, and even of the different cases, depend on the rapidity of the process. The more rapid the process becomes, the more complete the collapse and the less the edema. The slower the process is, the less the collapse, the more the edema and the greater the likelihood of the lung being invaded, even if the condition is not infectious in origin.

As a basis of discussion of pulmonary atelectasis, from the standpoint of its particular features, one should emphasize that the term "pulmonary collapse" should be restricted to the reversal of a fetal state of the lungs, namely, collapse of air spaces as well as vessels. Such collapse of the lungs is produced during life either by pneumothorax or by occlusion of a pulmonary artery. Any other form of pulmonary collapse is never a real collapse; it is "atelectasis." The degrees of atelectasis show great variations even in the same pulmonary processes of exactly the same etiology, and the anatomic features vary accordingly.

There is not the least dispute over the anatomic structure of the type of atelectasis which is generally understood by this term. All those describing its morphology, uniformly emphasize the lack of air and the marked dilatation of the pulmonary vessels, especially that of the capillaries which are filled with blood. The bronchioles are filled with serofibrinous exudate and frothy seromucous fluid. The pulmonary tissues are markedly edematous. The atelectatic lung shows different degrees of shrinkage, but is never collapsed to more than half of its original volume, frequently considerably less. The atelectatic lung is full of blood in its vascular bed and full of serum in its air passages. This explains its volume and weight. In short, the pathologic process in atelectasis is that of edema localized to greater or lesser areas of the lungs. In general edema of the lungs, collapse is usually even less than in partial edema, because compensatory areas are always present which hold a great deal of air in stagnant emphysema. However, the conception of complete airlessness in atelectasis is wrong. A part of the air depot is squeezed out of the atelectatic lung, but a great deal of the air remains and is dissolved in the fluid contents of the air passages; hence, the frothy foamy consistency of the contents of these air passages. The atelectatic lung even retains some degree of motility, as is evident from the roentgen observation of its paradox excursion during expiration. That the atelectatic lung still transmits considerable volumes of

blood is evident from the cyanosis present clinically. The amount of blood transmitted through an atelectatic area is also the index of the extent and intensity of the atelectasis. From the investigations of Andrus [6] one knows that immediately after atelectasis the blocked lung still transmits about 30 per cent of the blood. From the investigations of Binger, Erich and Christie [7] one learns that the circulation through pneumonic lungs is completely blocked, and that here atelectasis is therefore complete and immobilization and consolidation perfect.

Another form of atelectasis is that produced by infections. This, too, shows a wide range of variations from simple infectious edema to frank pneumonia. Here the question hinges on the age-old dispute of the differentiation between transudate and exudate. It is evident that the difficulty lies in the fact that there are no leaps in nature, transition is too smooth for sharp demarcations. Some pathologists make arbitrary delineations, and insist on sharp discrimination on the basis of morphologic features. Some authorities of international reputation say that they are at a loss when it comes to the drawing of a line of demarcation between simple and infectious edema of the lungs. In simple edema one finds exudation of fibrin, leukocytes and erythrocytes with desquamated epithelial cells. In infections, exudation frequently stops just at this point and does not go on to hepatization. The distention of the alveoli and compression of the blood vessels in inflammatory conditions contrast with the collapse of the alveoli and dilatation of the blood vessels in edema, but there are exceptions even to this. As Loeschke [8] pointed out, in inflammatory conditions, too, one frequently finds the alveoli collapsed. The alveoli are distended by the coagulation of the exudate. In atelectasis, coagulation of the transudate does not usually take place, but even this may occur in atelectasis from bronchial obstruction, in which the air passages are so blocked that their contents cannot be discharged. In complete permanent occlusion of a bronchus, collapse does not take place until the coagulated transudate has been absorbed. Even in pneumonic processes, the first stage, before red hepatization, is just an excessive engorgement with edema. Even in frank lobar pneumonia the marginal areas are in a condition of simple collateral edema and atelectasis.

The relationship between atelectasis and inflammatory processes of the lungs has been defined in a most elucidating manner by Loeschke.[8] This German pathologist, who has a great reputation, has described

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6. Andrus, W. deW.: Cardiorespiratory Physiology Following Collapse of One Lung by Bronchial Ligation, Arch. Surg. **10**:506 (Jan.) 1925.

7. Binger, C. A. L.; Erich, W., and Christie, R. V.: Klin. Wchnschr. **7**:33, 1928.

8. Loeschke, H.: Monatschr. f. Kinderh. **41**:135, 1928.

inflammatory processes as hypertelectatic, dystelectatic and atelectatic conditions, to which differences he attaches pathogenetic significance. According to Loeschke, croupous pneumonia is hypertelectatic, the exudate is here primary in the alveoli, which are therefore found in distention. In bronchopneumonia, on the other hand, which begins in the terminal bronchioli, the air passages are blocked first; the alveoli are therefore partially or totally collapsed and one finds dystelectasis or atelectasis. The inference I draw from this is that in pneumonia the process is so severe that the entire area of the lungs becomes involved almost at once, and exudation is so excessive that it reaches all alveoli before they can collapse. In bronchopneumonia, a central area is first involved, and obstruction of air passages causes collapse of alveoli before the exudate can reach them.

The pathologic dispute over the line of demarcation between edema and inflammation is hottest in the question of the chronic localized edemas found at autopsy in patients who did not show any clinical signs of pulmonary disease. Prominent pathologists frequently diagnose such edemas as pneumonia. As a matter of fact, their frequently long duration predisposes to some infectious invasion, and the differentiation is then hopeless.

From this discussion one may safely conclude that the pathologic anatomic substrate of respiratory failure is atelectasis of the affected area of the lung. The pathologic anatomic substrate of all pulmonary diseases, regardless of etiology, is pulmonary atelectasis of variable degree and intensity.

CLINICAL CONSIDERATIONS

In a discussion of pulmonary atelectasis from the clinical standpoint, I should begin by pointing out that atelectasis is to some extent a physiologic condition. It is frequently observed over different areas of the lungs at examination of healthy persons. Even marked degrees of atelectases may be observed, without clinical significance, in bedridden patients with competent circulation, if they are kept on their back for longer periods. Considerable degrees of atelectasis can be demonstrated in persons with markedly poor breathing by the tympany and râles which clear up after vigorous respiration.

Clinically, atelectasis shows a wide range of variations in degree, according to the pulmonary diseases but there is no disease of the lungs in which some degree of it could not be demonstrated. The most generalized forms of atelectasis are seen in acute suffocations, hanging, drowning and gassing. Massive total collapse is also a generalized form of atelectasis, which one should define as aborted pulmonary edema, the process being so abrupt that there is no time for frank edema to develop. Another generalized form of pulmonary atelectasis is present

in pulmonary anaphylaxis, in which the lungs are distended instead of collapsed because the process is so general, and in which the struggle between atelectasis and obstructive emphysema is so widely diffused that the fatal issue takes place even before the lungs could collapse. Another generalized form of pulmonary atelectasis is present in infectious congestions, the "fluxions" or the "fluxions poitrine" of the French clinicians. Milder types of generalized atelectasis are invariably present in miliary disseminations of infections, carcinoses and silicoses, in extensive pleural adhesions, emphysemas, diffuse bronchial processes (bronchiolitis) and other conditions.

Partial pulmonary atelectasis accompanies all local diseases of the lungs. I have observed it with great regularity in severe tuberculous lesions. It has been reported in pyogenic infections of the lungs. Recent investigations proved it to be the underlying factor of postoperative pulmonary complications. It is generally known as the outcome of all bronchial obstructions from foreign body aspiration or tumors, etc. Isolated patches of atelectasis are invariably seen about acute pulmonary lesions of whatever etiology. As such lesions never come to autopsy, the dispute is hot over their interpretation. Some call them perifocal inflammations, others think they are collateral edemas. Clinically, one frequently sees these areas disappear almost as abruptly as they came; when persistent, however, they may be infected and subsequently become a part of the lesion. As a rule the more severe the lesion, the greater is the atelectatic patch, and vice versa.

The mechanism producing atelectasis in all these clinical processes, regardless of their etiology, is, of course, the same. It is either failing respiratory function, by way of direct immobilization or by way of excessive compensation, which fails. The workings of this mechanism are plainly in evidence in all diseases of the lungs. The most clearcut picture of this mechanism is presented by the clinical entity of "massive collapse." In massive collapse, functional failure of greater or lesser areas of the lungs arises abruptly. There is a sudden closing down of ventilation at a time when considerable pulmonary plethora has been raised just previously. A respiratory crisis is precipitated, in which according to the severity of the condition greater or lesser areas of the lungs are abandoned to collapse, in order that the rest may take advantage of all available ventilatory capacity. The exact sequence of events is, of course, still a question that remains to be solved by future observations of the circumstances in which it arises. However, there are some suggestive points that should serve as points of departure for such investigations.

It is generally known that immediately after operations, especially under anesthesia, catarrhal phenomena are usually present in the lungs,

which betray the foregone plethora. The so-called "wet anesthesias" are merely more marked forms of this phenomenon. It is also a well known fact, that during most operations the patients hyperventilate, either because of the anesthesia or because of the anxiety. The pulmonary plethora is evident in the marked facial flush of these patients. In the presence of great pulmonary plethora, hyperventilation must be kept up on the top level, unfalteringly and steadily. Even the shortest interruption in ventilatory pace is most likely immediately to embarrass transmission of the large pulmonary blood depot. Reduction in ventilatory pace must be slow and gradual under such circumstances; otherwise it will precipitate a respiratory crisis. If under such circumstances wrong posture, smothering by covering of the face, abrupt increase of intensity of narcosis to the point of respiratory depression and other factors suddenly interfere with the ventilatory pace, respiratory failure of greater or lesser severity is produced. Under less severe conditions a timely compensatory effort saves the situation, preventing total collapse of the lungs by sacrificing some of the areas. Even under these circumstances all of the pulmonary areas are not involved to an equal extent. By abandoning to atelectatic collapse the most involved areas, the dangerous plethora is abducted through these areas, and the other areas have an opportunity to pick up in function. Probably, the leakage of serum is also the way by which dangerous plethora is reduced when respiratory excursions are so low as to fail to transmit the blood depot through the lesser circuit.

As to the bronchial plug theory of massive collapse, I think it is so untenable that it is not even worth discussion. I will, however, point out some of its inconsistencies for the sake of throwing some additional light on this interesting condition. As many workers have pointed out repeatedly, the most acute and fatal cases do not show any trace of a bronchial plug and are so abrupt that there could be no time for the absorption of the air; yet atelectasis is complete. Already Archibald[9] raised the question, where does the vast amount of fluid come from if the bronchus is plugged? The question may be asked, where does the material which goes to make the plug come from? Bronchial obstruction causes only obstructive emphysema. In the animals in which it was thus possible to produce atelectasis, respiratory function was so impaired that the animals were incapable of normal response and could not raise any emphysema. The conception of absorption of the air behind the plug is all wrong. In the first place, the air passages in atelectasis contain a considerable amount of air dis-

9. Archibald, E. W.: Extrapleural Thoracoplasty in Treatment of Pulmonary Tuberculosis, Arch. Surg. **10**:328 (Jan.) 1925.

solved in the frothy foamy fluids, for what else could be the cause of this frothy foamy consistency of the bronchial contents? The conception of air absorption by the circulation is based on the experiments of Lichtheim [10] who showed that atelectasis cannot be produced if, simultaneously with bronchial obstruction, the corresponding pulmonary artery is ligated. This experiment of Lichtheim does not prove that the air is absorbed by the circulation. As a matter of fact, the only thing this Lichtheim experiment does prove is just my contention that atelectasis depends on the production of excessive pulmonary plethora. What Lichtheim did by the simultaneous ligation of the pulmonary artery was the prevention of pulmonary plethora in the obstructed lung by cutting off its blood supply completely. Of course, this will prevent atelectasis, but not because the air cannot be absorbed. It was pointed out by workers repeatedly, and the scrutiny of the clinical features of massive collapse plainly show that the condition is a general respiratory distress affecting the entire lung; hence the frequency of multiple localizations. Could they all be plugged at once? To finish the discussion of massive collapse I shall point out, that while the condition is general, the great frequency of it in lower lobes, and especially that at the right side, is explained by the downflow of the bronchial contents, or transudations, into these lower parts of the lungs. This additional fluid accomplishes the drowning of these lobes much sooner than would take place otherwise. The same occurs in pulmonary hemorrhage.

The clinical presentation of pulmonary atelectasis—respiratory failure—must include at least a few remarks on the symptomatology. The physical signs of atelectasis show variations, from dull tympany to marked flatness; from the finest clicks to crepitation, rattles, and the peculiar suction sounds which were described by Williams (as quoted by Gairdner) as "clicking valve like sounds." The roentgen phenomena also show a wide range of variations, from most intense opacity to just heavy cloudiness.

The subjective clinical phenomena of respiratory failure become manifest only when embarrassing proportions of the breathing surface or a severe form of ventilatory disturbance is affecting the lungs generally. The clinical symptoms of respiratory failure may arise acutely or develop in chronic progressive form. The cardinal symptoms of the "respiratory failure syndrome" are as follows:

1. Flush of the skin, especially that of face and neck, is frequently associated with chill. This flush I have found to be associated with the first phenomenon of respiratory failure, pulmonary plethora. In every condition in which pulmonary plethora exists I have invariably

10. Lichtheim, L.: Arch. f. exper. Path. u. Pharmakol. **10**:54, 1878.

observed a facial flush. It is present in exercise exhaustion, in every acute pulmonary condition, from pneumonia and influenza, to massive collapse.

2. Dyspnea marks the degree of pulmonary plethora at which capillary engorgement has developed, and alveolar function is interfered with.

3. Cyanosis means transmission of unsaturated blood amounting to 6.7 per cent (Lundsgaard and van Slyke) of the total circulatory volume. It may be due to decreased ventilation or passage of blood through an atelectatic area.

4. Increases in the pulse and respiratory rate are phenomena of the compensation effort.

5. Cough and expectoration are due to the transudations into the tissues or even the air passages.

6. Cold sweats are probably due to a compensation effort for loss of pulmonary evaporating surface.

This symptom-complex takes on agonizing proportions in severe forms of respiratory failure. Under such circumstances circulatory decompensation phenomena become manifest, and the similarity to the condition of circulatory failure is great; hence, the traditional confusion of respiratory failure with circulatory failure. From the foregoing it is evident, however, that in respiratory failure it is pulmonary function that comes first to a stop. The circulation is then stopped short within the lesser circuit. Thus, death in respiratory failure is a genuine pulmonary failure, and not a cardiac failure.

THERAPEUTIC CONSIDERATIONS

I shall finish this discussion with remarks on the therapeutic side of the question. It should be emphasized here, that therapeutic results, when direct and clearcut, are the clinicians evidences to the correctness of his working theories and conclusions. They should be regarded as equivalent to experimental evidences. My contention that pulmonary atelectasis as it occurs in most pulmonary diseases is the pathologic substrate of respiratory failure is fully borne out by the results of all modern treatments for pulmonary diseases. Most of the methods are actually based on these principles.

To begin with, the most clearcut form of atelectasis is "massive collapse," and its prevention lies in obviating respiratory failure by artificial stimulation of respiration in form of inhalations of carbon dioxide. This is also the most successful treatment for this condition.

In a recent publication, Henderson and Haggard [11] recommended inhalations of carbon dioxide as a prophylactic measure against all pneumonic processes and as a procedure which has been found to be effective in all such conditions known to cause pneumonia, such as postoperative states, asphyxias from gas, etc. The effect of inhalations of carbon dioxide under such circumstances is the establishment and maintenance of ventilation adequate to the existing pulmonary plethora and assurance of the transmission of the accumulated volumes of blood.

In all critical stages of diseases of the lungs I employ artificial stimulation and support of respiratory function with oxygen inhalations. In conditions in which respiratory compensation effort is deficient, this method is helpful. Frequently, however, I have a situation in which overcompensation is the cause of a respiratory crisis, and in which stimulation is harmful. I see this conspicuously in the critical stages of pneumonia, in which the way of relief lies rather in depression of respiration, or reduction of pulmonary plethora. The salutary effect of morphine in just such critical pneumonias has always been a puzzle. The question has been investigated recently by Binger and Davis [12] by means of exact gas analyses carried out on a large number of patients with pneumonia. These workers concluded that "the benefits obtained from administration of morphine by way of relief of distress, reduction of metabolism, gain of sleep, outweigh the ill effects of reduction in ventilation, and increase of anoxemia." It is evident that in the critical stage of pneumonia the pulmonary plethora is to be combated even at the price of increasing anoxemia. My most excellent weapon in the combat against pulmonary plethora is bleeding. The effects of a copious phlebotomy in critical cases of pneumonia are frequently nothing short of miraculous. It is to be regretted that this powerful weapon of the therapeutic armamentarium of the fathers of medicine has gone out of fashion in modern medicine. Phlebotomy tackles the trouble at its root, and reduces venous return and with it also pulmonary plethora. Phlebotomy is the most effective treatment in a respiratory crisis of whatever etiology; it is the supreme treatment for pulmonary edema.

The modern methods of treatment for chronic diseases of the lungs have snatched the secret of nature; they are doing the same thing more effectively. As was shown in this discussion, the natural tendency is to eliminate the affected part from function. In the presence of extensive lesions, however, nature meets with insurmountable difficulties, and here is where one's methods come to the aid of nature and achieve collapse of the affected parts. The effect of these procedures lies in

11. Henderson, Yandell, and Haggard, H. W.: Hyperventilation of the Lungs as a Prophylactic Measure for Pneumonia, J. A. M. A. **92**:434 (Feb. 9) 1929.

12. Binger, C. A. L., and Davis, J. S., Jr.: J. Clin. Investigation **6**:171, 1928.

the additional room that is thus provided for compensatory expansion of the hyperfunctioning parts of the lungs. This is what saves the life of a patient whose great pleural effusion is aspirated. This effect is expressed in the tremendous extensions of lung volume of the functioning side in therapeutic pneumothorax, thoracoplasty, etc. The effect is also manifest in the failures of these procedures. Pneumothorax of too great pressure or a defective functioning lung that cannot take advantage of the opportunity for expansion offered are the causes of the failures. It is a well observed roentgen phenomenon in collapse therapy, that after each successive collapse the opacity of the functioning lung is increased at first. The reason for this is that after each collapse of the affected side, pulmonary plethora is produced in the unaffected side. But if pneumothorax pressure is not too high, and the lung is under no handicap (lesions or adhesions), the former resiliency is soon regained and even increased by further expansion and compensation. In pneumothorax work, this is the most reliable guide. Refilling should not be employed until the good lung has regained its former resiliency and production of collapse should cease when the functioning lung stops taking advantage of the opportunity for expansion offered. The respiratory failures arising after most successful surgical collapses are due to the failure of the functioning side to take advantage of the opportunity for expansion.

Compensatory expansion is the only way to combat respiratory failure. In all clinical conditions of respiratory failure, pulmonary edema is produced because of lack of compensatory expansion, either because there is not sufficient room or because there is not sufficient respiratory stimulus. Some patients with pneumonia die because they cannot effect sufficient respiratory compensation; others, because the solidified unyielding lung is in the way of proper compensatory expansion. The most clearcut evidence of this is the fact that even most desperate forms of respiratory failure may be successfully combated by the maintenance of respiratory expansions. Haven Emerson [13] showed that persons with pulmonary edema may be successfully treated by artificial respiration, and he proposed this method for all forms of pulmonary edema in man.

CONCLUSIONS

All pulmonary diseases, regardless of their etiology—mechanical, infectious or nervous—produce respiratory failure, either localized in a restricted pulmonary area or general failure of the entire lung. The functional pathologic substrate of respiratory failure is pulmonary

13. Emerson, Haven: Artificial Respiration in the Treatment of Edema of the Lungs, Arch. Int. Med. **3**:368 (May) 1909.

atelectasis. The pathologic anatomic substrate of respiratory failure is pulmonary edema.

The clinical substrate of respiratory failure is the "respiratory failure syndrome."

Death in respiratory failure is death caused by apnea. The circulation is stopped short within the lesser circuit.

CAVERNOUS HEMANGIOMA OF THE SCROTUM

REPORT OF A CASE*

NATHAN WINSLOW, M.D.

BALTIMORE

Cavernous hemangioma of the scrotum is a comparatively rare disease. Including Robert's case, described by Boullay, in 1851, I can find only ten cases listed in the literature. Of these, four were cited by Curling, as early as 1866, in the third edition of his monograph on diseases of the testis. Since then, as far as I am aware, no attempt has been made to consolidate the knowledge concerning this lesion. As I have recently had a patient with one of these neoplasms, it has occurred to me that a survey of the literature, with a brief history of my patient, should prove of interest, especially as modern textbooks give practically no consideration to the subject. Wyeth, in his "Text-Book of Surgery," disposed of the condition by saying that it occurs. Johnson, in his "Surgical Diagnosis," described a case, and Young, in his "Practice of Urology," said that two such cases were observed in his clinic at the Johns Hopkins Hospital, but he stated none of the details. All of the other books that I consulted did not mention the subject.

REPORT OF CASE

A white boy, aged 17, entered the hospital on Feb. 1, 1926, complaining of a lump in the right side of his scrotum which he had first noticed five months earlier, following a kick received while playing football. At that time the tumor was small; from the beginning, however, it grew slowly though steadily, until it attained the size of an orange. It had caused him no inconvenience other than a dragging sensation when he was on his feet. The growth was ovoid and reached above almost to the external abdominal ring, where it merged with the cord. The overlying skin was normal in color and healthy, but was thrown into corrugations by the underlying mass, to which it was lightly bound. A normal testicle could be distinctly felt at the bottom of the scrotum just behind the lower end of the swelling. The neoplasm gave the impression of being composed of a congeries of blood vessels, matted and intermingled in the utmost confusion. It was tender on pressure, and did not visibly decrease in volume when the patient lay on his back. It did not pulsate, and no bruit could be heard. The contents of the left scrotal sac were normal. While the picture was unusual, it bore no resemblance to that of a hernia, for which the boy had been sent to the hospital, or to a varicocele. As the patient had undergone seven operations at the Johns Hopkins Hospital for angiomas of the right leg, the first of which was performed four years and the last two years ago, this was thought to be a similar condition, and was diagnosed as such.

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* Submitted for publication, April 29, 1929.

* From the Surgical Department, University of Maryland.

Operation.—Operation was performed on February 2, with the patient under gas and ether anesthesia. The tumor was dissected out en masse through an incision 3 inches (7.6 cm.) long in the anterior surface of the scrotum. As soon as the subcutaneous tissues were reached, a conglomeration of dilated, tortuous veins and arterioles, incompletely surrounding the cord and testicle, came into view. Here and there vascular offshoots were sent into the skin. The bulk of the mass, however, was located beneath the skin. The tumor was supplied by two veins, located deep in the perineum, running in the groove between the rectum and the root of the penis. These were doubly tied and divided. The growth was

Cavernous hemangioma of the scrotum.

separated without much difficulty from the surrounding structures, and was removed. It was in no wise connected with the vessels of the cord.

Dr. W. J. Carson, at the time on the staff of the pathologic department of the University of Maryland, to whom the specimen was sent for microscopic examination, reported as follows: "Section shows the mass to be made up of a large number of dilated veins filled with red blood cells and a moderate number of arterioles, several of which contained organized thrombi." From this picture, he rendered a diagnosis of cavernous hemangioma of the scrotum with organized thrombi.

The postoperative course was uneventful, and the boy was discharged from the hospital on February 27 as cured. He was reexamined recently. The cure has persisted.

CASES CITED IN THE LITERATURE

Boullay described an erectile, subcutaneous neoplasm removed by Robert[1] from the scrotum of a man, aged 20, which had existed for twelve years. At the time of its onset the patient felt a sudden, abrupt pain in the right side of the scrotum, without known cause. Since that time his health had always been good, but the tumor had gradually increased in size. On the right side of the scrotum was an ovoid, bossellated mass. The skin was unchanged in color, but one could see beneath it a violaceous tint. No bruit could be detected. The cord and testicle were distinctly recognized. The excised mass consisted of dilated, erectile veins.

Ricord[2] described a case in a man, aged 29, who was admitted to the hospital on Nov. 20, 1855, with a tumor the size of the fist in the right side of the scrotum. It appeared to be congenital. When the patient was 11 years of age and again when he was 19, it became painful and inflamed without apparent cause. Nine years later, a third inflammatory crisis occurred. As the size of the tumor did not subside under treatment, the man decided to have it removed. The growth was ovoid and measured 20 cm. in length and 8 cm. in breadth. It extended up to the external inguinal ring and surrounded the right testicle and spermatic cord. The skin was not discolored. It was hard and did not fluctuate. There were no appreciable beats or bruit recognizable by the ear or by touch. Ricord could not recognize the cord or the testicle. He diagnosed the condition as an erectile, venous tumor of the scrotum, and on November 29, with the patient under chloroform anesthesia, he proceeded to enucleate and excise it. The man was discharged as cured on Jan. 5, 1856. A microscopic examination made by Verneuil showed the growth to be an erectile, vascular neoplasm which had undergone inflammatory changes. It contained a number of small cysts filled with a serosanguineous fluid.

Holmes[3] reported the case of a boy, aged 10, who was admitted to the hospital on May 1, 1862, with a congenital, venous tumor of the scrotum. At first the growth had remained more or less stationary in size, but later it had increased decidedly; the growth was accompanied by the escape of blood from the urethra, though not in large quantities. The skin was intact and healthy over it, but it presented the venous color plainly. On palpation, numerous masses, more or less round and hard, could be felt. The cord could not be traced below the external ring, where it seemed to be lost in the mass. Nothing could be felt but a congeries of greatly enlarged veins. There was no pulsation. On the other side, the scrotum and testicle were healthy. A short time after the patient was admitted to the hospital, Dr. H. C. Johnson proceeded to operate by passing three ligatures as deeply as possible under the mass, and tying them tightly around the tumor and skin. This procedure diminished the bulk somewhat and appeared to have entirely checked its growth. On September 1, the boy was discharged as greatly benefited. After this operation, there was no recurrence of bleeding from the urethra. He was readmitted, however, on Jan. 20, 1863, when he was placed under Dr. Holmes' care. It was then thought best to place a ligature around the base of the tumor. Two needles were accordingly passed in, at right angles,

1. Robert, in Boullay: Bull Soc. anat. de Paris **26**:194, 1851.

2. Ricord, in Verneuil: Note sur une variété rare et peu connué de tumeur des enveloppes scrotales; tumeur érectile veineuse congénitale developpée dans le tissu celulaire des bourses, Gaz. hebd. de méd. **6**:581, 1859.

3. Holmes, T.: Tumor of the Scrotum in a Boy, Tr. Path. Soc. Lond. **15**:95, 1863-1864.

through the base of the tumor, as deeply as possible, and an india rubber band was applied over them. This band gradually entered the scrotum to some distance, but did not divide the whole of the base of the swelling. The suppuration excited in the track of the needles was thought to have had considerable effect in consolidating the vessels at the base of the neoplasm. In July, 1864, there had been no fresh increase in the size of the growth. At that time, the testicle could be plainly felt lying at the top of the tumor.

Hewett[4] mentioned having been called on to treat a patient who had a congenital, vascular tumor of the scrotum in which the arteries were universally enlarged, some of them being the size of the radial, and from which alarming hemorrhage had taken place. The growth was arrested and cure obtained by subcutaneous ligatures.

Rivington[5] reported the case of a man, aged 23, who was admitted to the hospital on Jan. 16, 1875. A tumor larger than a hen's egg occupied the posterior part of the left side of the scrotum and extended into the perineum. Over the surface of the swelling, dilated veins were observed. To the touch, the tumor felt as if it was composed of enlarged veins mingled with little nodules of fibrous tissue scattered through it. At first the patient attributed it to a blow that he had received on the testicle a week before his admission. He said that he had never noticed a tumor in the scrotum before the injury, and that it had appeared suddenly after the blow and had not increased in size. According to the father, when the patient was 10 years of age he had received a blow in the same spot from his brother's knee; that the part had swelled, and that he had had leeches applied to the scrotum. Under this treatment the swelling subsided. The patient verified his father's statement, and said that the swelling had never wholly disappeared after the first injury. It seemed, therefore, most probable that the tumor was congenital, although it may have increased in size in consequence of the blows inflicted on it. On Jan. 28, 1875, the tumor was removed en masse, the surgeon making a longitudinal incision over it and dissecting it out. The cure was complete. Microscopic examination disclosed veins irregularly dilated. Small collections of fat and connective tissue were intermingled with the vessels. The structure was not that of an ordinary venous nevus.

King[6] described the case of a white boy, aged 3 years and 3 months, with an enlargement in the left inguinal region which occurred suddenly and was accompanied by pain. He saw the patient on May 15, 1893, and three days thereafter, when the operation was performed, he thought the tumor had increased to twice its former proportions. The case presented all the symptoms of a left, complete, irreducible, inguinal hernia. A herniotomy incision revealed a venous mass knotted and twisted on itself; so much did it resemble an intestine that, had not the signs of strangulation been absent, it could easily have been mistaken for a gangrenous intestine. The dilatation of the vein began about one-half inch (1.27 cm.) to the left of the symphysis pubis and filled the left side of the scrotum. The convolutions were contracted to the size of a goose-quill at certain intervals and at other points dilated to the size of the little finger. The growth was found

4. Hewett, in discussion on Holmes: Tr. Path. Soc. Lond. **15**:95, 1863-1864.

5. Rivington: Vascular Tumor of the Scrotum; Removal; Recovery; Remarks, Lancet **2**:608, 1877.

6. King, G.: An Uncommon Venous Tumor of the Scrotum, Alabama M. & S. Age **7**:238, 1894-1895.

to empty into a single vein. This was ligated. The entire mass was then removed. It had no connection with the spermatic vessels. The patient was permanently cured.

In 1908, Johnson[7] removed a congenital cavernous angioma of the scrotum from a man, aged 26. The tumor had existed and grown steadily, though slowly, as long as the patient could remember. The mass of dilated veins and trabeculated blood spaces was as large as two fists when the patient stood erect. The venous channels communicated with two large veins running into the perineum in the angle between the bulb of the corpus spongiosum and the rectum. An illustration accompanying the article shows that the tumor was located on the left side.

Guardia[8] reported the case of a man, aged 45, who entered the hospital complaining of a tumor in the testicle. Since birth he had had in the scrotum a "small dilated vein" which had never troubled him until five years ago. Eight months before, the mass had become large and tender, and on one occasion a profuse hemorrhage occurred. On examining the genitalia, one found a circular, spongy, purplish mass, involving the skin and extending over the whole left side of the scrotum and the upper posterior third of the thigh. It could be decreased in size and blanched on pressure. No expansile pulsation or bruit could be determined. The tumor was excised under spinal anesthesia. It extended well into the deep layers of the periurethral and perianal tissues. The mother veins were the internal pudendals. The man was completely cured.

Young[9] furnished no detailed information concerning the two cases mentioned in his text. One he lists as case 7829. The patient was admitted to the Johns Hopkins Hospital for an angioma involving the scrotum, penis and the under surface of the thigh.

He dismissed the topic with the statement that hemangiomas in this region are rare venous varices, independent of varicocele, there having been only two cases in his clinic in which such varices involved the scrotum, penis and the under surface of the thigh. In the second instance,[10] the case is registered as case 8231. The treatment employed in both cases, though Young did not say so, was apparently excision of the vascular tumor.

COMMENT

Of the aforementioned cases, only eight are described in sufficient detail for analytic purposes. These show a striking similarity in the method of their onset, development and symptomatology. In all, the disease began during the first or second decade of life as a small growth which gradually but steadily increased in volume to a size varying between that of a hen's egg (Rivington's case) and that of two fists (Johnson's patient). Occasionally the onset was abrupt, without known cause; at other times, the lesion was attributed to an injury. In none

7. Johnson, A. B.: Angioma of the Scrotum, Surgical Diagnosis, ed. 2, New York, D. Appleton & Company, 1911, vol. 2, p. 713.

8. Guardia, J. de la: Cavernous Hemangioma of the Scrotum, Fourteenth Annual Report, United Fruit Company, Medical Department, 1925, p. 137.

9. Young, H. H.: Hemangioma of the Scrotum, Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 711; see illustration on p. 470.

10. Young (footnote 9; see illustration on p. 479).

of the patients was the general health affected. In King's patient there was local pain, and in my patient a dragging sensation when he was on his feet. Examination revealed a tumor occupying either the right or the left half of the scrotum, with the overlying skin thrown into a series of hummocky folds. The skin itself, however, was healthy, intact and of a natural color, though the contained blood might be seen glimmering through it as a bluish streak. In every instance, the growth was confined almost entirely to the subcutaneous tissues and had no connection with the spermatic vessels. It was always unilateral. In none were beats or bruit felt or heard. The neoplasm was ovoid and more or less hard and lumpy. All of the patients were cured by operative measures, either by subcutaneous ligation, as in Holmes' and Hewett's cases, or by excision en masse. A remarkable feature of Holmes' case was the escape of blood by the urethra; this bleeding ceased after the first operation, never to recur. The growth showed no preference as to the side on which it appeared. Of seven cases in which this feature was mentioned, the tumor occurred in the right scrotal sac in three cases and in the left in four cases. The ages of the patients ranged from 3¼ to 45 years, respectively. Of more significance, however, was the age at which the tumor appeared.

Guardia considered tumors of this type as vascular new growths and not dilatations of already existing vessels, as suggested by Adami. Mallory regarded them as the product of endothelioblasts, and classified them as endotheliomas. He thought that the growth begins in the veins rather than in the capillaries, and at first takes the form of endothelial folds supported by a small amount of connective tissue, thus resembling the valves of the normal veins. As the tumor continues to grow, it becomes thrown into numerous folds which obstruct and dilate the vessels until their walls give way to pressure and permit the angioblastic mass to escape and invade the adjacent tissue.

The treatment is complete eradication of the growth by excision.

While a vascular tumor of this type in the scrotum is at most a comparatively minor ailment, I believe the infrequency of its occurrence at this site is sufficient justification for placing an example on permanent record and for calling attention to the few cases in the literature.

SURGICAL WOUNDS IN HUMAN BEINGS

A HISTOLOGIC STUDY OF HEALING WITH PRACTICAL APPLICATIONS: I. EPITHELIAL HEALING *

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Accurate knowledge of the process of epithelial repair in wounds is essential to a proper understanding of the clinical treatment of surfaces over which it is desirable to procure a covering of epithelium. In a recent histologic study of eighty-nine surgical wounds in all stages of healing in human beings, it was found that there are two distinct types of healing, epithelial and fibrous. Neither of these types falls directly into the existing descriptions of methods of tissue repair as taught in textbooks. As the two types of healing are distinct processes, and but little related to each other, they will be described separately. This paper will be confined to a description of the healing of epithelium, with clinical application of the observations.

An extensive review of the literature relating to epithelium in wounds and epithelium in tissue culture was made. Some basic facts concerning the potentialities of the individual epithelial cell were uncovered, the knowledge of which is important in arriving at a conception of epithelial healing: 1. The epithelial cell is potentially a motile cell, capable of progression over a suitable surface. It moves by means of pseudopodia.[1] It grows in tissue culture in continuous or branched membranes, the peripheral cells of which present pseudopodic processes. 2. The form of the epithelial cell in cultures depends directly on the type of base on which it rests. In fluid it becomes spherical, on a fiber it becomes stretched out and closely applied to the fiber. Stationary on a flat surface, it is round with a round nucleus, but in motion the same cell may become very long, flat and elliptical. All of these facts must be borne in mind in the interpretation of histologic pictures of epithelium.

The distinctive feature about epithelial healing is that it is a true outgrowth of new tissue from preexistent, functioning tissue of like kind. Vascular endothelium, alimentary epithelium and probably

* Submitted for publication, May 29, 1929.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Fischer, A.: Tissue Culture, Copenhagen, Levin & Munksgaard, 1925, p. 107.

glandular structures apparently heal by means of the same type of process. Fibrous healing, on the other hand, takes place by the rapid production of a "fill" of new fibrous tissue between the severed portions of the preexisting fibrous structures, producing tissue union without true growth of new tissue from old tissue. Indeed, the term "growth" as applied to tissue is too loose a word to use with accuracy. It indicates only increase or enlargement without expressing the means of increase or enlargement.

The normal stratified squamous epithelium of the surface of the body is described in five layers; from without in (fig. 1) these are:

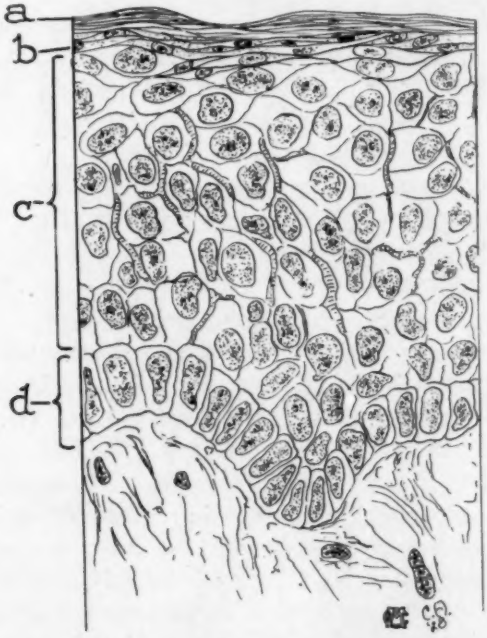

Fig. 1.—Normal human epithelium; *a*, cornified layer; *b*, granular layer; *c*, prickle cell layer, and *d*, basal cell layer; × 500.

(1) cornified, or keratinized layer (dead cells); (2) stratum lucidum (rarely evident on other than palmar and plantar surfaces, composed of dead cells, and not considered in this paper); (3) granular layer (dead or dying cells); (4) prickle cell layer, malpighian layer or stratum mucosum (by some the lowermost cells are considered the germinal layers), and (5) basal cell layer, or palisade layer (more commonly accepted as the true germinal layer from which all other layers arise).

It is the basal cell layer which lies in contact with the dermis of the skin and which is considered to consist of the least differentiated

and most primary epithelial cells. The overlying layers, then, are formed by differentiation of the more embryonic basal cell in the process of keratinization. It is strongly suggested by the observations made in these human wounds that the primary epithelial cell is not the basal cell, but is the prickle cell of the mucosal or malpighian layer.

Although such a conclusion seems radically at variance with the present teachings of histology, in the literature there is considerable support for it. Loeb, in 1892, arrived at the same conclusion after studying experimental wounds in guinea-pigs, and he and his associates have since done much work to substantiate it. In fact, these observations in human beings correspond almost exactly with those described by Loeb [2] in guinea-pigs and later in the rat and the pigeon.[3] As controls for these observations in human beings 101 wounds from one hour to fifteen days old were studied in guinea-pigs, rabbits, dogs and swine. The observations in the animals used as controls exactly paralleled those in human beings.

THE HEALING MEMBRANE

Grossly, about the margins of healing burns or ulcers there exists a thin membranous "outgrowth" of epithelium which lies on the denuded surface. In dry wounds this is usually adherent, but in wounds with considerable exudate it is possible to insert a thin instrument under this membrane and to lift it from its base. Such a "healing epithelial membrane" is found in all healing wounds, although its form may be greatly varied by local physical conditions, such as the type of surface it rests on and the amount of moisture in the wound. The mode of formation of this "healing membrane" and the factors influencing it are not generally understood and therefore bear description.

Perhaps the most common impression of the process of epithelial regeneration in healing of wounds is that, since the basal layer of the old epithelium is the regenerating layer, there occurs a rapid increase in mitotic division in the basal layer peripheral to the wound, which results in a large increase in epithelial cells about the margin of the wound. The new cells then get out in some way onto the surface of the wound as a direct extension of the surrounding basal layer. This primary basal layer then produces more cells which pile up above the basal layer to produce the normal prickle cell and granular and cornified layers of epithelium over the area of the wound. But this does not seem to be the process in human tissue.

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2. Loeb, Leo: Ueber Regeneration des Epithels, Arch. f. Entwcklngsmechn. d. Organ. **6**: 297, 1898.

3. Loeb, Leo: A Comparative Study of the Mechanism of Wound Healing, J. Med. Research **41**: 247, 1920.

Special Structure.—In a wound one day old, the bordering epithelium will be found beginning to cover the cut ends of the incised dermis. This "extension membrane" is not formed by a lateral outgrowth of the basal cell layer. Instead, the upper cells of the prickle cell layer become elongated, they extend down over the cut ends of the other epithelial layers and the most distal cells lie directly on the exposed dermic fibers. The topmost cells become cornified, with the result that there appears to be an active extension directly into the wound of the uppermost prickle cell, granular and cornified layers. Such a condition is shown in figure 2.

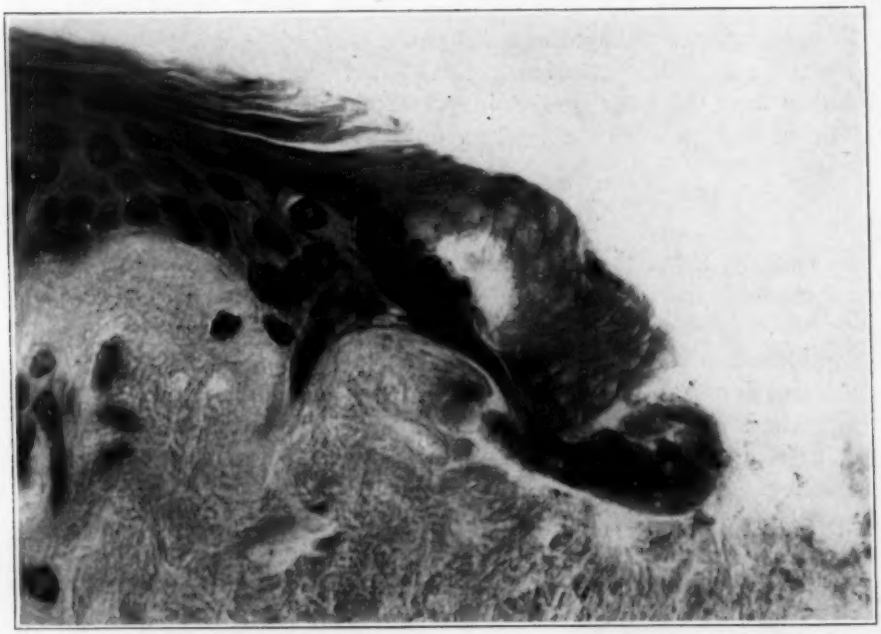

Fig. 2.—First stage of epithelial extension into a wound one day old, in a human being. There is elongation of the upper prickle cells with extension over other epithelial cells onto the denuded dermis; the exposed cells are cornified and there is no outgrowth of a basal layer; × 700.

By the time three days have passed, this extension of the epithelium may reach for a considerable distance over the denuded dermis; in figure 3 is shown a typical advancing epithelial membrane. Such a membrane is always closely applied to an underlying base. It is thinnest at the end most advanced into the wound and is as thick as the old epithelium where it arises from the old epithelium. At its point of origin it still appears to be a direct continuation of the upper layers of the old epithelium. Cornified material overlies it for most of its length. According to the usual criteria of form and staining qualities of

epithelial cells, the cells composing the membrane should be highly differentiated, squamous, pavement cells and they should be either dead or dying, like the granular cells of the old skin. Such a membrane, however, or some variation of it, is the only structure that is constant in wounds that are known to be healing. The cells that appear dead are therefore very much alive and active. The cells themselves are long and flat and stain darkly; their long rodlike nuclei stain very darkly. Aside from the shape of the cells in the membrane, the two most striking observations are that it appears to arise by an elongation and movement outward of the uppermost cells of the old

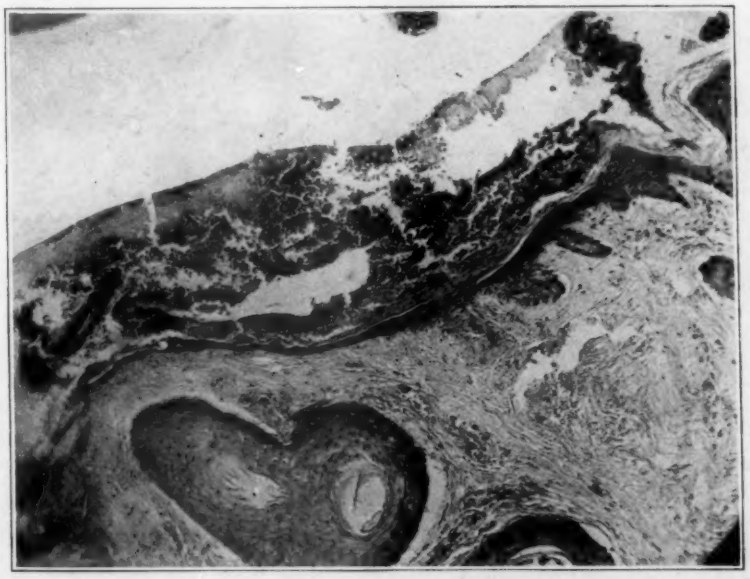

Fig. 3.—Typical epithelial healing membrane on compact fibrous tissue in a wound three days old, in a human being. The membrane adheres to the underlying surface and is continuous with the upper cells in the old epithelium. There is no basal layer and cornified cells overlie the membrane. A thick layer of purulent débris overlies the epithelium; × 60.

epithelium, and that there is under it no semblance of a basal layer of cells. A third observation, namely, that mitotic figures are nowhere to be found either in the old or in the new epithelium, indicates that the membrane is formed by the preformed cells of the old epithelium which actually move out over the defect. Applying here the fact ascertained by tissue culture, that the shape of the cell depends on its supporting structure and rate of motion, the conclusion is reached that the long, flat appearance of the cells of the membrane is due to their being cells that are in active motion into the wound.

Such a conclusion is substantiated by the finding of rather typical, round, pale, epithelial cells clumped at the end of a membrane, or in depressions under it in places of evident stagnation. Such cells must arise from the long, flat membrane cells for they have no other means of arrival at their situations, nor any connection with the old epithelium than through the membrane itself. Even where such rounded cells pile up, as in the older portion of the membrane or in depressions under it, there may be no evidence of a basal layer. Thus, all the epithelial cells in the area of the wound arrive at their ultimate situations by means of their movement into the wound from the old

Fig. 4.—Higher magnification of section in figure 3, showing the typical appearance of cells of the membrane, the direction of axes of cells in the membrane, absence of a basal cell layer and cornified cells overlying the membrane. The membrane is advancing from right to left; × 900.

epithelium, through the healing membrane. That this is so is shown also by the axes of the cells. In the old epithelium they overlap in a manner such that their axes point toward the membrane, whereas in the distal membrane the reverse is true; each cell next the dermis appears to have passed above the cells next nearest the old epithelium and then in turn to have come to rest itself on the fibrous base (fig. 4).

Origin of New Basal Layer.—A basal layer appears under the membrane late in the process of healing. The new basal cell layer

occurs in areas of cellular stagnation under the advancing membrane, where the deeper lying cells of the membrane have become rounded. This observation is of great interest. Since the cells in the membrane are derived chiefly from the preexistent cells of the upper layers of the old epithelium, and since the epithelial cells in the wound all are derived from such a source, unless a basal layer, as such, grows out from the old epithelium secondarily and under the membrane, whatever basal layer is formed under the new epithelium must be derived from the prickle cells of the old skin. There is no indication that there is at any time a true lateral extension of cells of the old basal layer other than that such cells may occasionally contribute to the formation of the membrane. Thus, the newly formed basal layer is derived from preformed prickle cells which have actively wandered into the denuded area. In the healing of wounds, therefore, the prickle cell must be considered the primary epithelial cell.

Occurrence of Mitosis.—After the wound is closed over with epithelium, or after about the fifth day, increasing numbers of mitotic figures may be found. The great majority of these are in the old epithelium, and they are by no means confined to the basal layer of the old epithelium. Likewise, under the older portions of the membrane, mitotic figures may be found in stagnant cells, but not in great numbers. Once the two membranes from opposite sides have united, the creation of the normal epithelial structure over the wound takes place by a continued increase of cells in the wound both by migration of cells from the borders of the wound and by local multiplication of cells.

The covering of a surface with epithelium is due, therefore, primarily to the motion of cells, and mitosis is of secondary importance in the essential process of covering the denuded area with epithelium.

Factors Influencing the Rate of Epithelial Outgrowth.—One characteristic of the epithelial membrane must be stressed. It always follows the available base. This in itself strongly points toward the extension of the membrane as due to ameboid motion, for it is inconceivable that cells move by themselves, without support. Tissue culture proves a base to be necessary for the motion of cells. If the cells were simply "juggled" out into the wound by tension existing in the old epithelium, or merely pushed out by rapid increase of their numbers, it would not be likely that they would always cling to the underlying structures as they do.

The tendency to follow the available base is so great that the membrane will advance in whatever direction the base leads, even though it lead directly away from the opposite side of the wound. Thus, every crevice and split in the underlying dermis or scar tissue becomes covered with epithelium and underlying spaces are prevented. If the membrane meets a mass of cellular or fibrinous débris which

offers several surfaces over which to advance, it will split and follow all of them. In this manner, eventually the tips of the two opposite membranes come in contact with each other over some surface, no matter how irregular, which extends from one epithelial margin to the other.

The type of base underlying the membrane appears to influence the form of the cells of the membrane and at the same time the rate of advance of the tip of the membrane into the wound. The membrane on compact fibrous tissue, such as that seen in figure 3, is

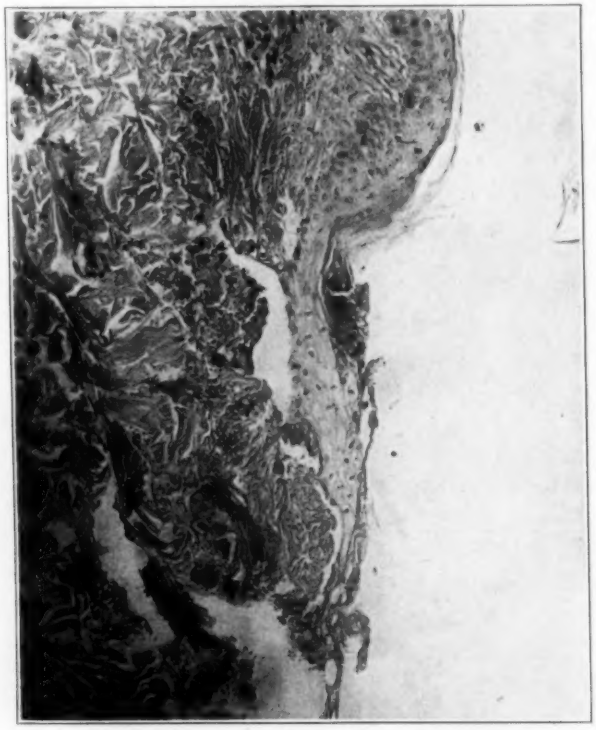

Fig. 5.—A typical epithelial membrane on a loosely compacted base in a wound three days old, in a human being. A short membrane and swollen cells are shown, and there is absence of a basal cell layer; × 80.

long and thin, with long flat cells. If the advance is made over a poorly compacted base, whether dermis itself or "scab," the cells are less long and flat and the membrane as a whole is shorter (fig. 5). Fat tissue not covered with connective tissue fibers appears to be inimical to normal epithelial progression, for membranes on fat are very short and "swollen"; although two membranes are united over a short length of intervening fat, a basal layer does not appear even after seventy-three days.

The tendency of the epithelium to follow the available base leads to an interesting observation (fig. 6). In all of the wounds examined, the epithelium dipped directly into the incision over the cut ends of the dermis for a variable distance. This distance was determined chiefly by how much fat or new fibrous tissue was pushed up between the dermic ends from the subcutaneous tissues. As for any healing activity in the dermic ends themselves, there is none. They are inert.

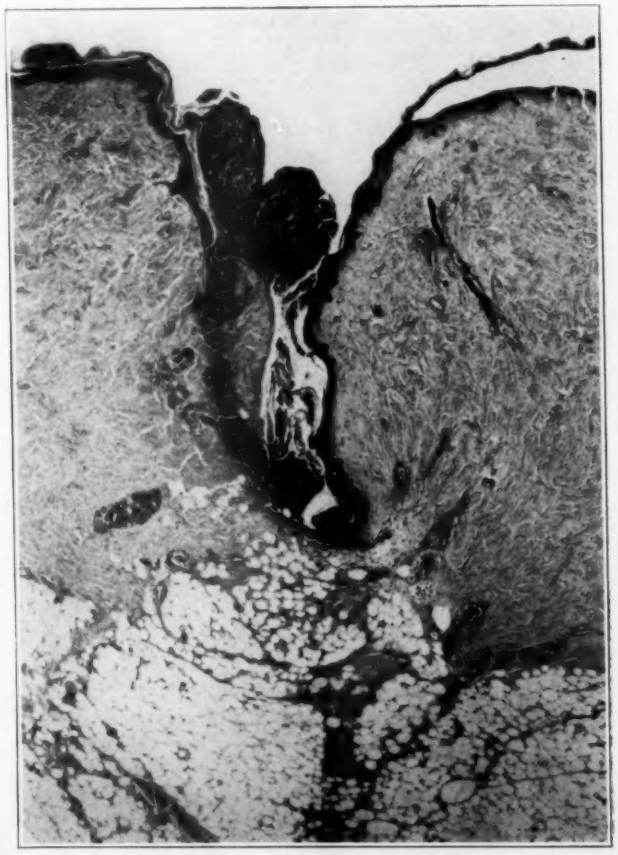

Fig. 6.—Transverse view of an apparently well healed incision ten days old, in human skin. The epithelium dips deeply into the incision, resting on the ends of the dermis, and the dermal ends are inert; × 18.

From such observations it must be concluded that one of the chief factors determining the rate of advance of an epithelial membrane is the type of base over which the membrane must progress. Closely compacted fibrous tissue appears to be the optimal base. Fat is the least favorable base.

Curiously enough, cornified material (fig. 4) overlies all but the most recent portions of the advancing membrane, giving the appearance of active extension of the cornified layer of the old epithelium into the wound. Such an active function for a dead structure is inconceivable. The more probable explanation is that cornification is related to the exposure of cells and the resultant cellular death. As the cells form the membrane, the topmost cells become exposed, with the result that they die and become cornified. The accretion of newly exposed cells at the terminal end of the cornified layer thus produces the appearance of active extension of the cornified layer into the wound.

From these observations another factor determining the rate of epithelial advance can be derived. Cornification or hardening of the exposed cells follows the advance of the membrane. This process demands the death of the cell, and this promptly removes the cell from those moving into the defect. If the amount of cornification is increased,

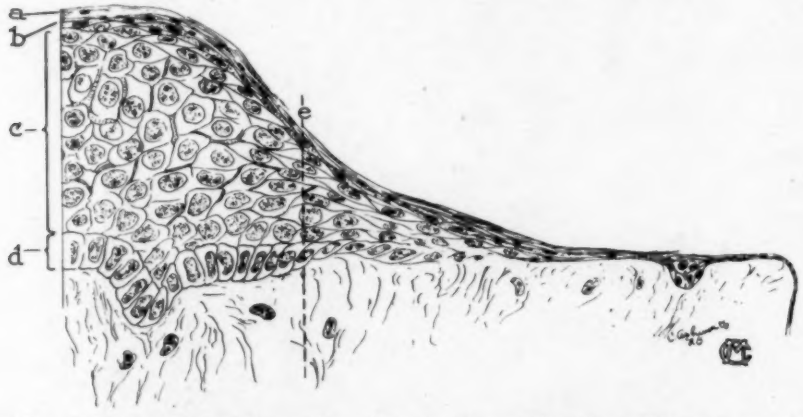

Fig. 7.—The mode of formation of the healing epithelial membrane in wounds of human beings. The drawing shows the origin of membrane cells from prickle cells, cornification of the topmost or exposed membrane cells, producing a direct continuation of cornification into the wound, rounding up of cells in stagnant areas under the membrane and the membrane following the available base. *a* indicates cornified layer; *b*, granular layer, *c*, prickle cell layer; *d*, basal cell layer, and *e*, point of incision.

it is obvious that the rate of advance of the membrane must suffer. The rate of cornification of the cells of the membrane, therefore, must be considered an important factor in the rate of epithelial outgrowth. Figure 7 is a diagram of the healing membrane, showing its various characteristics.

CLINICAL APPLICATIONS

The two factors which determine the rate of epithelial advance are susceptible to variation by clinical treatment. Indeed these two

factors must be the basis of many well established clinical precepts of the management of wounds which have been arrived at empirically. In the first place, infected wounds are known to obtain their covering of epithelium more slowly than clean wounds. Under the microscope, three conditions obtain in infected wounds in greatly exaggerated degree: 1. There is an increased number of cornified cells overlying the healing epithelial membrane. 2. There is likely to be loose granulation tissue, presenting a greatly increased surface to be covered by the advancing membrane, with the additional hazard of many deep clefts which must be filled with stagnant cells of the membrane before the membrane can proceed in its further advance into the wound proper. 3. There is likley to be much loosely compacted wound débris, over or through which the branches of the membrane will grow, only to be lost when the débris sloughs off or is torn off in the dressing of the wound, or over which the normal epithelial layered arrangement does not take place. At once, the actual effect of infection on the epithelium in a wound becomes translated into the two factors which determine the rate of the process of covering with epithelium; these are the rate of cornification of the advancing cells and the material and structure of the base presenting for the support of the advancing membrane.

From such a correlation of clinical and histologic observations, it must be assumed that the best way to hasten the process of covering with epithelium is to secure in a wound conditions the chemistry and physics of which provide the least amount of exposure inimical to the continued life of the advancing cells of the membrane, thus reducing the rate of cornification in the membrane, and to provide a suitable base for the epithelium to adhere to and to move on. It is probable that all wound dressings have their good or ill effect according as they fulfil such requirements. Any increased rate of healing after treatment is due to the reduction of conditions inimical to the epithelial advance, thus permitting the epithelium to "grow" at its optimal rate.

There is nothing new in the suggestion that the type of base determines successful epithelial outgrowth. In skin grafting with Reverdin or Thiersch grafts it always has been stressed that the base must clinically be "clean and healthy," and free from infection, and fluid must not be allowed to collect between the epithelium and the base. Moist dressings are carefully applied so as to reduce to a minimum the amount of exposure of the healing cells.

Again, it is doubtful that anything so drastic as the application of the cautery to the edge of a delicate epithelial membrane is actually stimulating to the cells of that membrane. Cauterization coagulates the accumulated serum and the loosely grouped granulations, thus providing in another manner a suitable, compact base for epithelial

progression. Various methods of applying pressure and protection, such as adhesive tape, petrolatum, gauze, sponges, etc., all fulfil the same ends.

Thus, the benefit, if any, of any particular method of wound dressing may be looked for in its action toward procuring: (1) a satisfactory base for the epithelium to wander out on, and (2) physical and chemical protection for the cells of the membrane against an inimical environment which would cause increased cornification of the healing cells.

As Mills [4] has said concerning this work, it "has much to do with the histogenesis of epithelial tumors of the skin." Later, Dr. Mills intends to publish the results of his investigation in this field.

CONCLUSIONS

1. The living cells of normal human epithelium are potentially ameboid cells.

2. In the healing of wounds covering with epithelium takes place through the ameboid movement into the wound of cells from the surrounding epithelium. Such moving cells form an "extension membrane." The process of covering with epithelium is completed by the union of two such membranes from opposite sides of the wound, followed by the rearrangement and multiplication of the cells of the membrane.

3. Mitosis occurs secondarily to cellular movement and late in the process of healing.

4. The majority of the cells which form the extension membrane are derived from the prickle cell layer of the old epithelium.

5. A basal cell layer is formed under the epithelial outgrowth by a rounding up and alinement of the lowermost cells of the membrane, rather than by outgrowth of cells from the old basal layer.

6. The prickle cell of the normal epithelium is therefore capable of becoming the basal cell in the epithelium of the scar and must be considered the primary cell in the regeneration of epithelium in the healing of wounds.

7. The formation of the healing epithelial membrane is dependent on a supporting base suitable for the movement of epithelial cells.

8. The base available for the support and advance of the epithelial membrane is the chief factor determining the time and place of the union of the epithelium from the two sides of the wound.

9. The rate of cornification of cells of the membrane is also a determining factor in the rate of the process of covering with epithelium.

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4. Mills, R. C.: Discussion, Proc. Staff Meetings Mayo Clinic **3**: 247, 1928.

10. The chief causes of delayed epithelial healing, therefore, are the existence of a supporting wound surface unsuitable for progression of epithelial cells, and rapid cornification of the cells of the membrane due to inimical chemical or physical environment. The conditions just named are accentuated in infected wounds.

11. Any beneficial effect of a particular method of dressing wounds may be referred to its action toward producing a more suitable base or more suitable environment in which the epithelial cells may grow out normally.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

A SERIES OF FOURTEEN CASES *

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The present study is based on a series of fourteen cases of primary carcinoma of the fallopian tube. This is, we believe, the largest series that has yet been studied in any one clinic. Five of the patients were in the Johns Hopkins Hospital; the remainder were operated on in neighboring hospitals, all but two by members of our staff, and the operative specimens were brought to this hospital for study. Seven of these cases have already been reported at various times by Hurdon,[1] Vest [2] and Cullen.[3] In order to bring the series down to date and complete it, the entire group has been included and studied in this summary. It is fortunate that we have been able to obtain fairly complete clinical and pathologic data and follow-up records in every case.

FREQUENCY

Primary carcinoma of the fallopian tube is one of the rarest of gynecologic conditions. In 1925, Liang [4] collected reports of 214 cases from the entire medical literature. Since that time, additional cases

* Submitted for publication, June 12, 1929.

* Read before the Baltimore City Medical Society, Jan. 18, 1929.

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1. Hurdon, Elizabeth: A Case of Primary Adenocarcinoma of the Fallopian Tube, Bull. Johns Hopkins Hosp. **12**:315 (Oct.) 1901.

2. Vest, Cecil W.: A Clinical Study of Primary Carcinoma of the Fallopian Tube, Bull. Johns Hopkins Hosp. **25**:305 (Oct.) 1914. Malignant Growths in the Fallopian Tube, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., Prior Publishing Co., 1928, vol. 11, chapter 25.

3. Cullen, Thomas S.: Carcinoma of the Right Fallopian Tube Readily Palpable through the Abdomen, Bull. Johns Hopkins Hosp. **22**:20 (Jan.) 1911; Primary Carcinoma of the Right Fallopian Tube, ibid. **16**:397 (Dec.) 1905.

4. Liang, Zue: Was lehrt das primäre tubencarcinom in pathologischer Hinsicht? Virchows Arch. f. path. Anat. **259**:577, 1926.

have been reported by Barrows [5] (3), Covarrubias [6] (1), Heil [7] (1), Kurtz [8] (1), Bower and Clark [9] (1), Vest [2] (1), Callahan [10] (1), Bültemann [11] (1), Kittler [12] (1), Cameron [13] (2) Stanca [14] (1) and Scott and Oliver [15] (2), a total of 16 cases. Including all, there are probably not more than 230 cases on record.

It is interesting to compare the incidence of primary tubal cancer with that of other gynecologic diseases. In the Johns Hopkins Hospital, for example, in 35,000 patients with gynecologic conditions there have been only 5 cases. In 1927, Barrows [5] stated that there had been only 3 cases in a series of 30,000 patients with gynecologic conditions treated in the Bellevue Hospital of New York. S. J. Cameron [13] of Glasgow remarked in 1925 that primary carcinoma of the fallopian tube was such a rare condition that many gynecologists had never encountered it.

RACIAL PREDISPOSITION AND AGE

Liang brought forward the observation that of 214 cases, reports of which he had collected, 107 occurred in Germany, 26 in France, 23 in England, 13 in Austria, 8 in Hungary, 6 in Russia, 5 in America and the remainder in various other European countries. It is difficult to believe that this observation has any significance as far as racial susceptibility is concerned; we rather think that it merely indicates the relative regularity with which gynecologists and pathologists in various

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5. Barrows, D. N.: Primary Carcinoma of the Fallopian Tube, with Report of Three Cases, Am. J. Obst. & Gynec. **13**:710, 1927.

6. Covarrubias, P. Alvaro, and Albertz, Arturo: Carcinoma de la trompa de fallopio (Case), Bol. Soc. de cir. de Chile **4**:188, 1926.

7. Heil, K.: Primäres tubenkarcinom, Zentralbl. f. Gynäk. **50**:2952, 1926.

8. Kurtz, H.: Fall von einem einseitigen primären tubenkarcinom ausgezeichnet durch das vorhandsein zahlreicher riesenzellähnlicher Gebilde, Ztschr. f. Geburtsh. u. Gynäk. **90**:133, 1926.

9. Bower, J. O., and Clark, J. H.: Primary Bilateral Carcinoma of the Fallopian Tubes; Recognition of Early Metastasis Essential to Successful Treatment; Report of a Case, Arch. Surg. **11**:586 (Oct.) 1925.

10. Callahan, W. P.; Schlitz, B. A., and Hellwig, A.: Primary Carcinoma of the Fallopian Tubes Associated with Tuberculosis, Surg. Gynec. Obst. **48**:14 (Jan.) 1929.

11. Bültemann, H.: Primary Cancer of the Fallopian Tubes, Zentralbl. f. Gynäk. **51**:1037, 1927.

12. Kittler, E.: Primäres tubenkarzinom mit impmetastase auf dem endometrium, Zentralbl. f. Gynäk. **51**:971, 1927.

13. Cameron, S. J.: Malignant Disease of the Ovaries and Fallopian Tubes, Brit. M. J. **2**:285, 1925.

14. Stanca, Constantine: Primary Cancer of the Fallopian Tube, Gaz. d. hôp. **100**:1155 (Aug. 31) 1927.

15. Scott, E., and Oliver, M.: Primary Carcinoma of the Fallopian Tubes, J. Lab. & Clin. Med. **14**:429 (Feb.) 1929.

countries record their unusual cases. Since 1925, 6 new cases have been reported in Germany and 14 (including the present series) in America.

The age incidence is about the same as it is for carcinoma in general, most of the cases occurring between the ages of 40 and 60. One case was observed in a woman, aged 70, and one in a woman of 25 (Bower and Clark [9]).

PREDISPOSING FACTORS

Salpingitis.—In 1895, Sänger and Barth stated that primary carcinoma of the fallopian tube had its origin in the irritation produced by chronic salpingitis, and since that time much evidence has been advanced to support or refute this supposition. The proponents of this theory point to the fact that in a large number of cases there are definite signs of chronic tubal inflammation. Thus, in one of the cases that we are reporting (31798), it is certain that the patient had had salpingitis for at least four years, undoubtedly of gonorrheal origin. Four of our fourteen patients had salpingitis at the time of operation. Cameron recalled the unusual coincidence of pyosalpinx and cancer in a patient operated on by Lawson Tait.

It is impossible, however, to determine the number of cases in which salpingitis has preceded the development of carcinoma, not only because of the lack of detailed histories in the recorded cases, but also because the tumor itself may produce a chronic inflammatory reaction, which, according to Doran,[16] may close the tube and simulate hydrosalpinx. Although four of our cases showed tubal inflammation at the time of operation, in only one were we certain that the salpingitis was an independent process which had antedated the development of malignant disease. The relationship between cancer and tuberculosis is even more remote, for only six cases are on record in which these conditions existed simultaneously in the fallopian tube. Even if in every case it could be demonstrated that tubal cancer had been preceded by chronic salpingitis, one could hardly draw any definite conclusions because of the extreme disparity in the frequency of the two diseases, cancer being the rarest and salpingitis the commonest of tubal diseases. After careful study of all of the recorded cases, Wechsler,[17] Vest and also Liang apparently hesitate to accept the opinion of Barth and Sänger. It seems to us, also, that one would hardly be justified in assuming that salpingitis plays any notable rôle as a precancerous lesion, although it is impossible to deny that chronic irritation may precede malignant metaplasia.

There is, however, another side to the question. For if chronic salpingitis may possibly be an unfavorable factor which predisposes

16. Doran, Alban: A Table of Over Fifty Complete Cases of Primary Cancer of the Fallopian Tube, J. Obst. & Gynæc. Brit. Emp. **6**:285 (Oct.) 1904.

17. Wechsler, H. F.: Primary Carcinoma of the Fallopian Tubes, Arch. Path. **2**:161 (Aug.) 1926.

toward cancer, it also plays the favorable rôle of setting up an effective temporary barrier against the early dissemination of the malignant growth by closing the tubal ostium.

When the tube is sealed, the growth may assume enormous proportions and many months may pass before it breaks through the tubal walls. On the contrary, if the tube is open, bits of the cancer escape into the peritoneal cavity early in the course of the disease, and this dissemination soon causes death. Furthermore, the pressure of the fluid and the tumor in closed tubes causes sharp pain and forces the patient to seek medical assistance quickly; when the tube is open, however, there may be no definite symptoms until the abdomen begins to enlarge because of ascites and peritoneal metastasis. Hence, we feel that in such cases salpingitis may prove to be a blessing, though considerably disguised.

It is interesting to contrast the uterine and tubal epithelium as regards other factors that might be concerned in the development of cancer in view of its frequency in the one and its rarity in the other organ. Both tissues arise from the mullerian ducts. The uterine epithelium is extremely active and is always in a state of menstrual transition; it undergoes tremendous hypertrophy during pregnancy and is exposed to injury and trauma much more frequently than is the tubal mucosa. Moreover, there are three different types of uterine mucosa, and it is well known that carcinoma seems to have a tendency to develop at points where two types of epithelium meet. In contrast, the tubal epithelium is remarkably inactive and is well protected. Although it exhibits cyclic changes corresponding with the menstrual phenomena, they are slight. There is no recurring monthly desquamation and regeneration, and even during pregnancy the tubal mucosa alters little. Consequently, these circumstances produce a situation which offers scant opportunity for cellular overgrowth, hyperplasia or unusual cytologic activity. Whether or not these factors are of any consequence is merely a conjecture.

PATHOLOGY

Sänger and Barth divided primary tubal carcinoma into two types, papillary and papillo-alveolar, and this classification has been generally quoted. Friedenheim added a third, the alveolar wall type. In 1925, Liang made a careful pathologic study of the subject and arrived at the conclusion that the various types which Sänger, Barth and Friedenheim [18] had suggested were only stages of one process and did not represent real morphologic differences. He consequently contended that their classification was arbitrary and unnecessary. It is quite certain that in our

18. Friedenheim, Bernhard: Beitrag zur Lehre vom Tubencarcinom; Ueber ein primares rein alveolares Carcinom des Tubenwand, Berl. klin. Wchnschr. **36**:542 (June 19) 1899.

cases one can find all of the foregoing types represented, except the "alveolar wall" type of Friedenheim, which we have never seen. In almost every individual growth, moreover, there are areas that are distinctly papillary, others alveolar and others solid. On the basis of the cases we have studied, we agree with Liang that fundamentally the tumors are identical histologically, exhibiting only such minor varieties in growth and morphology as one would naturally expect. Furthermore, we have been able to offer no differentiation as to grades of malignancy, judging either from the histology of the growth or the clinical end-result. Although it may be true that some tumors are largely alveolar and others papillary, there is at present no evidence that they are inherently distinct or that their behavior is different in regard to malignancy, methods of extension or clinical characteristics. This phase of the subject merits further study as new series are reported.

The lesion is usually situated in the middle or outer third of the fallopian tube. Depending on the size of the growth and the patency of the fimbriated extremity, the gross appearance of the tube varies. If the abdominal ostium is closed, the tube may present every appearance of a hydrosalpinx, except that it is often bluish or purple, because of the dark color of the enclosed fluid. A coexistent salpingitis, pyosalpinx or tubo-ovarian cyst may completely mask the situation. The tube is often adherent. On opening it, one finds the pale, papillary growths of variable size. Some of them are attached by such slender pedicles that they break off and float out with the dark, coffee-colored fluid. When the tubal ostium is open, these masses may be clearly visible at the fimbriated extremity. In such cases, one usually finds peritoneal metastases and at times ascites.

The neoplasm has its origin in the mucous membrane of the tube. Various stages of metaplasia may be observed in any one case. In some areas the tubal epithelium is markedly hyperplastic, and small papillary growths replace the fine wavy tufts of normal mucosa. In these papillae, there is little connective tissue framework, the growth consisting chiefly of single layers of tubal epithelium, arranged in glandlike pattern, suggesting the picture found in adenocarcinoma of the endometrium. The epithelial cells themselves show no abnormal change, but the pattern shows malignant disease.

In other papillae in which the process is further advanced, there is a heaping up of the epithelium so that it may be several layers thick or may even form solid nests of cells. The cells become more and more irregular in shape and atypical, and the nuclei are hyperchromatic. One could entertain no doubt as to the presence of a malignant condition in these papillae.

As the papillae enlarge and press against each other, they unite to form solid masses of tissue. The alveoli are filled with a hyaline secre-

tion, and the papillae tend to lose their individuality. Mitotic figures, lymphocytic infiltration and occasional areas of necrosis appear. This stage corresponds with the so-called papillo-alveolar type.

In primary carcinoma, the tubal growth is predominantly inward, toward the tubal lumen, and the masses usually fill the tube and distend it before there is the slightest tendency to invade the muscularis. This was the situation in all of our cases. In one, reported by Cullen, the tube formed a large cystic mass that reached the umbilicus and was filled with fluid and carcinoma (fig. 2); yet, in spite of the size of the growth, the tubal wall was everywhere intact, although it was so stretched that it was only 2 or 3 mm. thick. In advanced cases, the tumor may invade the adjacent tubal wall superficially; as a rule, however, metastases occur elsewhere long before that happens (figs. 1, 2, 3, 4 and 10). This is, indeed, a most striking phenomenon and has led some observers to doubt the malignancy of the tumor; a casual perusal of the end-results, however, even in apparently hopeful cases, discredits any such supposition.

Carcinoma of the tube is often bilateral. In 183 cases, Wechsler found the growth on the right side in 64, on the left in 62 and bilateral in 57. There are, moreover, various indications which suggest that both tubes are involved more often than we suppose. In some cases in which the growth is apparently unilateral (Liang 2 cases and Wharton and Krock, 1), there is a suspicious papillary hyperplasia of the mucosa in the supposedly sound tube; furthermore, in some cases in which unilateral salpingectomy has been done, early recurrences have been observed in the tubes which looked normal and were not removed. In view of the established fact that the growth is often bilateral, both tubes should always be removed.

Metastasis occurs early and is widespread because of the many means of ready dissemination. When the tubal orifice is open, peritoneal implants occur early, and the disease rapidly reaches its fatal termination. When the fimbriated extremity is closed, the growth may remain limited to the tubal mucosa for months and eventually spread by direct extension to the mesosalpinx, the adherent ovary, the uterus and peritoneum or be carried to more distant organs by the lymphatics or the blood stream. Rarely, as in one of our cases (34,144), are implants observed in the endometrium; when diagnostic curettage has been done in such cases, the pathologist's report on the curettings has been adenocarcinoma of the body of the uterus, a correct but somewhat incomplete verdict. Implants are prone to occur in the abdominal scar or in the vaginal drainage tract. The pelvis is rich in lymphatics, and metastases have been observed in the inguinal, lumbar, sacral, hypogastric and external iliac glands. Rossinski reported an instance in which the

supraclavicular glands were involved. Secondary growths have also been noted in the liver and mammary glands.

It is interesting to compare primary with secondary tubal carcinoma, for they are unlike in every particular. Secondary cancer is more common than primary. It usually comes from the ovary, cervix or endometrium, and the picture of each is characteristic. In ovarian cancer, the growth may be by direct extension or by peritoneal or vascular dissemination. In carcinoma of the cervix, we have observed that the growth reaches the tube by the lymphatics, and that one finds small islands of typical squamous cancer in the tubal wall or mesosalpinx. In endometrial carcinoma, the tube may act as a channel for the transmis-

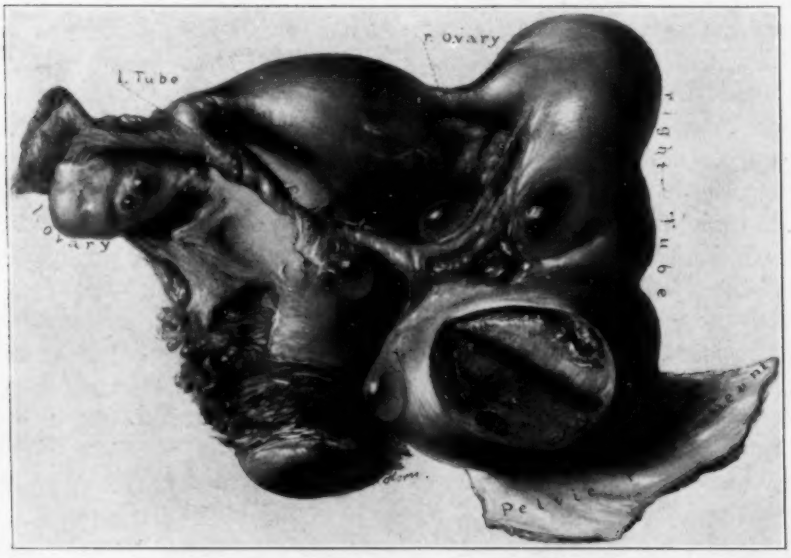

Fig. 1 (no. 8114).—Primary carcinoma of the right fallopian tube. The external resemblance to pyosalpinx should be noted. Carcinoma was recognized at operation, however, and an extremely wide dissection made (panhysterectomy, removal of six inches of bowel and adjacent pelvic peritoneum); recurrence and death in six months. (From Bull. Johns Hopkins Hosp., by courtesy of Dr. Thomas Cullen).

sion of malignant cells, as Sampson [19] has shown. In such cases, one finds the malignant tissue loose in the tubal cavity. It is conceivable that it might become fixed and grow on the tubal mucosa, although we have not yet observed this. None of these secondary tubal growths have the branching, treelike characteristics of primary cancer, nor do

19. Sampson, John A.: Peritoneal Endometriosis Due to the Menstrual Dissemination of Endometrial Tissue into the Peritoneal Cavity, Am. J. Obst. & Gynec. **14**:422 (Oct.) 1927.

they share its other manifestations. The striking difference between primary and secondary tubal carcinoma is the fact that primary cancer almost never invades the tubal wall, whereas secondary growths almost always start there.

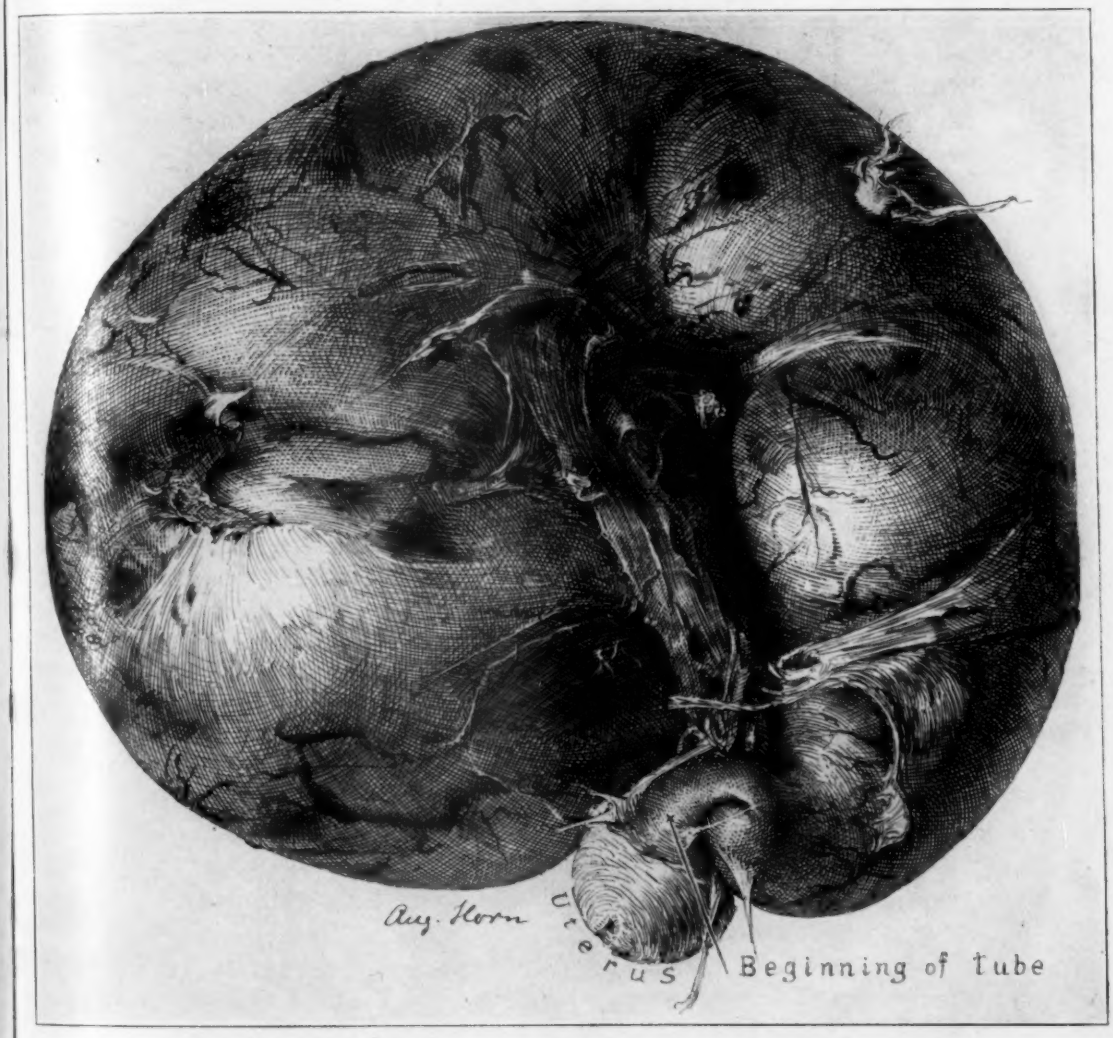

Fig. 2 (no. 11536).—Unusual case of primary carcinoma of the tube, reaching almost to the umbilicus. The tube wall is not invaded, even by a growth of this size. (From Bull. Johns Hopkins Hosp., by courtesy of Dr. Thomas Cullen).

THE CLINICAL PICTURE

It is hardly remarkable that no one has yet diagnosed primary tubal carcinoma before operation; indeed, in the vast majority of instances,

the condition has escaped recognition, even on the operating table. When the tube is closed, adherent, cystic and enlarged, the diagnosis of hydrosalpinx or pyosalpinx has been made. When it is evident that a malignant process is present, the diagnosis has usually been ovarian cancer or peritoneal or pelvic carcinosis. Although in some cases surgeons have recorded that the tube had unusual or peculiar characteristics, in few instances has it been stated that the diagnosis was made unqualifiedly without the aid of the microscope. Many times the malignant fallopian tube has been overlooked entirely, so intent has the operator been in removing a benign myoma or ovarian cyst. The gross appearance of the tube may certainly be most deceiving, but it is our impression that usually the correct pathologic diagnosis could be reached if the tube were opened and examined in the operating room. This might also have some bearing on the surgical treatment and possibly on the end-result.

The earliest and most constant symptom of primary carcinoma of the fallopian tube is pain. Vaginal discharges of various sorts—watery, purulent, leukorrheal or sanguineous—then appear. Menstrual disturbances, malaise, weakness, fever, dysuria, gastro-intestinal symptoms, abdominal enlargement and cachexia develop as the disease progresses.

Pain is the earliest symptom and is usually definite and severe. In this respect, carcinoma of the fallopian tube gives a danger signal much sooner than almost any other intraperitoneal malignant lesion. The pain is sharp and colicky, is usually located in the iliac fossae, and may be accompanied by nausea and vomiting. At times, it is sudden in onset. In many instances the sharp pain is superimposed on a dull pelvic discomfort which may have been present for years, due perhaps to preexistent salpingitis, ovarian cyst, injury at childbirth or myoma. The sharp pain recurs frequently for months, with increasing severity as the disease progresses.

The early onset of pain is probably due to the tension produced by the increasing secretion of fluid and the growing tumor within the closed tube. At times, pain is a late phenomenon, and then the earliest symptom may be an unusual vaginal discharge or abdominal enlargement due to ascites.

Vaginal discharge may appear early in the course of the disease. Almost every variety of discharge has been noted, the usual type being a watery or leukorrheal, blood-tinged fluid which is persistent. Foul-smelling, green, yellow and brown discharges have also been observed.

Because of such vaginal discharges in patients within the cancer age, curettage has frequently been performed. At times, polyps, myomas and benign endometrial changes are present to confuse the picture; under these circumstances, the persistence of the discharge after the correction of the uterine condition is extremely significant, and should direct one's attention to the adnexa. If curettage reveals no pathologic

endometrial change in a woman who has a sanguineous watery discharge, one should think of tubal carcinoma, particularly if other symptoms are present. Under these circumstances, the presence of an adnexal tumor is an indication for laparotomy.

Fig. 3 (no. 11536).—Cross-section of tumor in fig. 2, showing enormous dilatation of tube, intact thin walls, extensive malignant growth; recurrence in three and one-half years. (From Bull. Johns Hopkins Hosp., by courtesy of Dr. Thomas Cullen).

The amount of fluid that may be discharged per vaginam is amazing, in one instance being about a liter a day. Wechsler noted that the discharge may be periodic and may be accompanied by paroxysmal pelvic cramps which diminish or cease after the fluid escapes. In these cases,

the situation is apparently analogous to hydrops tubae profluens, in which the tubal secretions escape through the uterus into the vagina. Since in the majority of these instances the uterine epithelium is normal, one must suppose that the discharge has its source in the tube.

When the fimbriated extremity of the tube is open, the secretions carrying bits of carcinoma escape into the peritoneal cavity. Under such conditions peritoneal metastases appear early, and ascites may be the first symptom. It is noteworthy that the sharp colicky pain which usually forces surgical intervention may not be felt in cases in which the fallopian tube is patent.

Practically all patients with tubal carcinoma have an abnormal vaginal discharge.

The menses are often affected by the disease, and almost every type of menstrual irregularity has been observed. It is quite probable that at times the menstrual disturbances are attributable to coexistent conditions, such as myomas, salpingitis, menopause and ovarian cysts. In many instances, menstruation has not been disturbed.

The usual menstrual irregularities are menorrhagia and metrorrhagia, although temporary amenorrhea has been noted. Because of the menstrual irregularity, pain and adnexal tumor, tubal pregnancy has often been suspected, although the age of the patient frequently excludes this possibility. Intermenstrual bleeding may be profuse, but this is not the rule. Dysmenorrhea may or may not be present. Taken as a whole, the menstrual phenomena are variable and give little assistance in elucidating the situation.

Backache is rather common, as it is in all pelvic disorders.

Gastro-intestinal symptoms, while not uncommon, are not as prominent as those which have been enumerated. Nausea, vomiting, constipation and pain on defecation have been observed, and in the advanced states, abdominal swellings and masses occur.

Urinary symptoms may be marked. In one case (Amann), the only complaints were referred to the bladder. At times incontinence appears, without any metastatic lesion in the bladder or urethra. As a rule, however, dysuria, frequency and other urinary symptoms form a relatively minor part of the syndrome.

Contrary to the opinions of many observers, sterility has not been prominent in our cases. It has been repeatedly stated that sterility is common in women who subsequently develop tubal cancer, and this has been advanced to support the contention that salpingitis precedes the development of malignant disease. This is not our experience.

A glance at our summary shows that of the twelve women who were married, nine had conceived, the total number of pregnancies being forty-one. Of the fourteen miscarriages, all but two were admitted to have been induced. Only three patients had not conceived; of these, one

married after the age of 40, one contracted salpingitis immediately after marriage and in the third, the cause of the sterility through twenty-three years of married life was not explained. In this case, there was no salpingitis at the time of operation and the tubes were open. In these twelve cases, therefore, there were only two definite cases of sterility, and in only one of these was it due to salpingitis. In our experience, therefore, sterility is not a feature of these cases, and salpingitis is known to have preceded the carcinoma only once. In the majority, the child-bearing function has been essentially normal, in spite of the fact that three patients had myomas and one a large ovarian cyst. In this series there were two instances of "one child marriages," in one case apparently because of a large fibroid and in the other because of the development of an ovarian cyst.

PHYSICAL OBSERVATIONS

One is surprised at the lack of uniformity in the conditions found at pelvic examination. In the clearcut simple case, there is a solitary adnexal mass of variable size, which is usually soft, fixed and tender. At times this mass may be hard and may occupy the culdesac of Douglas; in a few instances, the tumor shows fluctuation. In advanced cases, the tubal mass fills the lower part of the abdomen and is accompanied by ascites. Glandular enlargement is present at times.

When the condition is complicated by myomas, ovarian cyst and pelvic infection, as it often is, the symptoms are immediately obscured, and the diagnosis becomes practically impossible. When, as has happened, obesity and local tenderness make it impossible to feel any tumor, one can be guided only by one's clinical judgment and by the process of elimination. In such cases, the association of lancinating, persistent pelvic pain with a blood-tinged vaginal discharge should suggest the presence of a definite pelvic disease which requires surgical exploration. This is particularly true if the patient is in the carcinoma age and previous curettage has revealed nothing.

One would have to search long to find a medical or surgical condition that has eluded diagnostic skill as completely as has tubal carcinoma, for there is only one observer who has claimed that he even thought of the correct diagnosis before operation. The reason for this is to be found in the extreme rarity of the condition and the absence of any characteristic signs.

We can conceive, however, of certain conditions under which one would be justified in making the diagnosis tentatively. The development of a profuse, blood-tinged vaginal discharge in a woman beyond the menopause immediately suggests carcinoma of the uterus. If by palpation and curettage the uterus is found normal, if there has been severe pelvic pain and if one can feel an adnexal mass, tubal carcinoma

should be considered as a possibility, although one must also think of neoplasms of the ovary and salpingitis, particularly tuberculous.

In younger women, the diagnosis is much more difficult, because of the great number of tubal, ovarian and uterine lesions that can produce the same symptoms. As a rule, however, the discharge is more profuse than in other adnexal conditions; the mass is usually softer than a pyosalpinx or ovarian neoplasm, and the history goes back farther than it does in ectopic pregnancy.

The difficulty of making the correct diagnosis is almost always magnified by the presence of other pelvic lesions. Some patients have been treated conservatively for acute salpingitis and pelvic peritonitis; they may have had these and may have been discharged from hospitals when they were convalescent, only to find that they had tubal carcinoma when abdominal section was performed later. Except in uncomplicated cases, we doubt seriously whether in the child-bearing period the disease can be diagnosed with certainty before operation, because of its extreme rarity and the protean character of its symptoms. In older women, the chance of accurate recognition is greater.

Even on the operating table, the disease has often eluded recognition. In many a case, the operator has performed a conservative unilateral salpingectomy and has closed the abdomen, believing that he has removed a pus tube. At times, the presence of malignant disease has not been suspected until the report from the pathologic laboratory has been received after the patient has left the hospital.

In most cases, the simple expedient of opening the fallopian tube in the operating room would probably establish the diagnosis.

TREATMENT

The only treatment which has proved successful has been surgical. The ideal treatment would be removal of both tubes, ovaries and the uterus by block dissection, giving as wide a margin to the growth as possible. Since both tubes are frequently involved, since metastases occur in the endometrium and because of the proximity of the ovaries, it is unwise to attempt to save any of these organs. The only hope lies in complete and early extirpation.

Radiotherapy has been tried in a few cases, usually with poor results. Bültemann (1927) irradiated a patient, aged 50 years, for one and one-half years under the impression that the bleeding and pelvic pain were due to carcinoma of the uterine body. This treatment apparently had no effect on the course of the disease. Postoperative irradiation has been employed at times, usually in hopeless situations, without benefit. As Burnam said, the condition is so rare that few radiologists have had occasion to treat it; hence, for the time being, this phase of the subject remains an open question.

If one were to base his prognosis entirely on the results of the past, it would be necessary to conclude that the outlook is almost hopeless. In 1926, Wechsler found only 6 three-year cures in about 200 cases.

In our series of fourteen cases, three patients have lived three, four and five years, respectively. Of these, one died apparently without recurrence five years after the operation; the second was well at the end of four years, and the third was well after three years had elapsed. Nine patients, however, died of recurrence, one four years after the operation. Two patients have not been observed long enough to warrant conclusions. It is obvious that these results are not satisfactory.

The high mortality seems to be due to several factors—the extreme malignancy of the tumor, late operation and incomplete operation.

Primary carcinoma of the fallopian tube is a highly malignant growth. The disease rapidly reaches the inoperable stage if the tubal ostium is open and peritoneal implantations occur. When dissemination is prevented by the closed fimbriated extremity, however, the growth may remain circumscribed for months or even a year or more, if one may measure the duration of the disease by the clinical symptoms.

Although the dismal surgical results of the past are due in large measure to the extreme malignancy of the growth, it seems to us that we should survey the situation carefully in the hope of discovering some way in which it might be improved. We are impressed by two other facts—first, that surgical intervention has often been tardy, and second, that the operative procedures have frequently been extremely conservative.

The delay in intervention is in many cases the result of the patient's procrastination. Frequently, however, the delay has been prolonged by the surgeon who little suspects that he is dealing with cancer, but believes that he is treating with commendable conservatism a benign inflammatory process. It must be remembered that in not a single instance has the correct diagnosis been made unreservedly before operation, although in many the presence of malignant disease has been suspected.

The large number of recurrences is also due in some measure to the conservative operation that has been done, for hysterectomy with removal of both tubes and ovaries has been performed in less than one third of all reported cases. In the remainder, the operative procedures have been variable—removal of part of one tube, unilateral salpingectomy, unilateral salpingo-oophorectomy, bilateral salpingo-oophorectomy and others. Since the tubal disease is often bilateral and may involve the uterus and ovaries, it is apparent that conservatism is futile.

It is quite probable that the surgical treatment would have been more uniformly radical if the operators had suspected the presence of a highly malignant disease. This situation could readily be corrected by the gross inspection of the tube in the operating room.

REPORT OF CASE

History.—Mrs. A. B., a housewife, aged 29, admitted to the Women's Hospital in November, 1926, had had excellent general health until the age of 16, when she was operated on for appendicitis and peritonitis. Following this, there was no abdominal discomfort until after marriage, in 1922. After this, recurring attacks of discomfort developed in the suprapubic region, associated with painful and

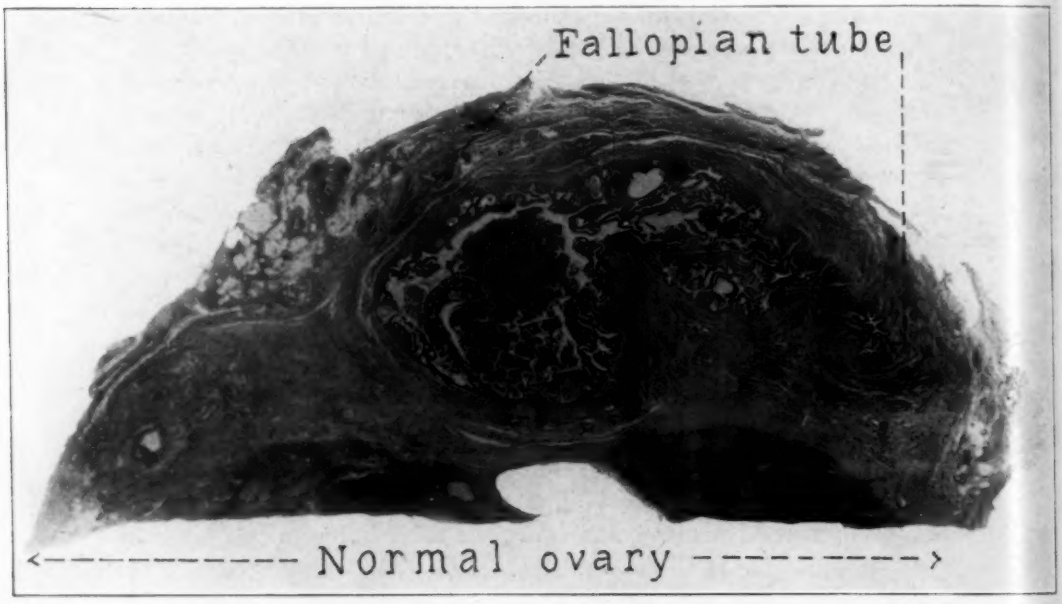

Fig. 4 (no. 31798).—Cross-section through the left tube and ovary; tubal lumen filled with carcinoma; no extension into muscularis or ovary; × 5.

frequent urination. There was no nausea or vomiting. During the last three or four months, the pain had become sharp and paroxysmal and localized in the left iliac fossa. Between these sharp attacks, there was a continual dull pelvic discomfort.

The patient had always had some leukorrhea, even as a young girl. Recently this had become profuse and malodorous, but never bloody or irritating.

Menstruation began at the age of 13. Until the past year, the interval had always been twenty-eight days, the flow lasting four or five. During the past year, the interval had been three weeks, without any other variation from the usual cycle. There had been no intermenstrual bleeding or menorrhagia. The menses were occasionally painful, but never excessively so.

Physical Examination.—The patient looked healthy and was well nourished; the skin was clear and the mucous membranes were a normal color. General medical examination gave negative results.

The abdominal examination gave negative results, except for distinct tenderness in the left lower quadrant. There was no mass, muscle spasm, rigidity or free fluid. The glands in the groin were not palpable. Pelvic examination revealed a profuse purulent discharge issuing from the cervix. The cervix itself was red and inflamed. Bartholin's and Skene's glands were normal. The uterus was normal in size, position and consistency, but its mobility was limited and painful.

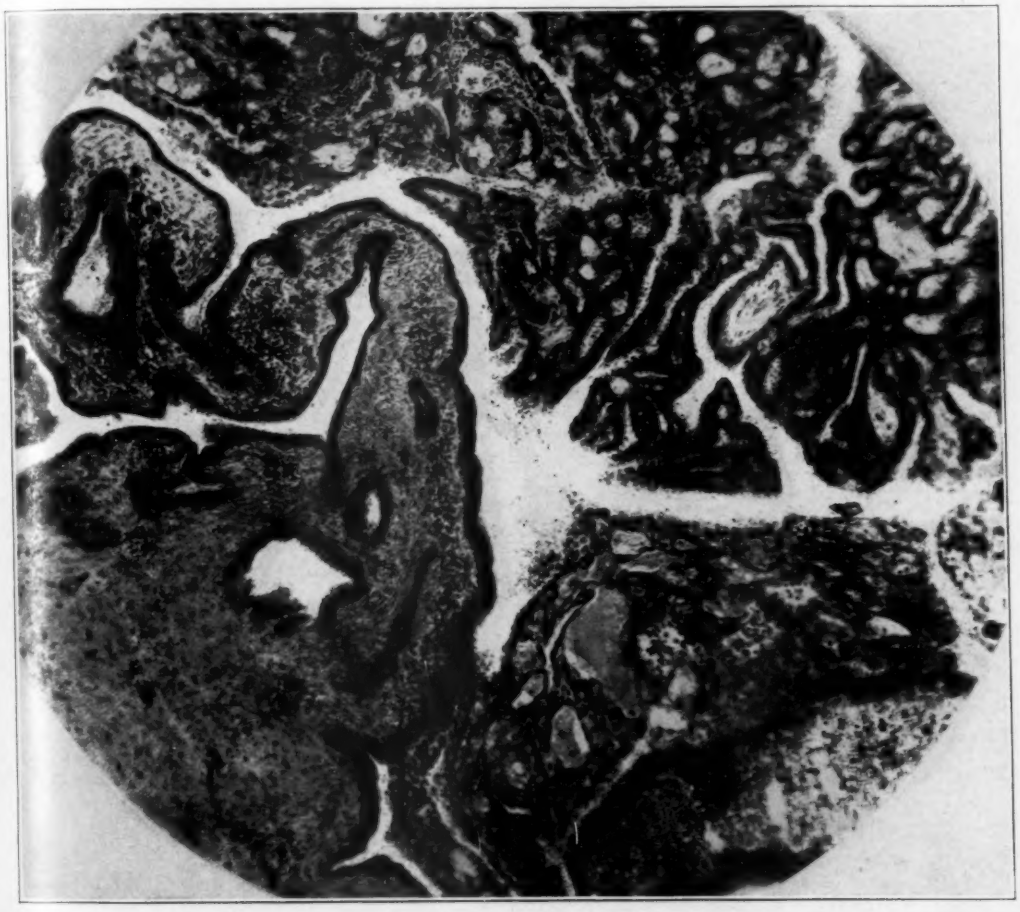

Fig. 5 (no. 31798).—Section through left tube showing three structures: (1) normal tubal papilla (left), malignant papilla (upper right) and solid carcinoma (lower right).

The adnexae were enlarged, adherent and sensitive. In the left fornix, there was a mass about 6 or 8 cm. in diameter.

Smears of the cervix showed that the pus contained some gram-negative diplococci. The catheterized urine was clear.

Treatment and Course.—The preoperative diagnosis was chronic salpingitis and cervicitis, probably gonorrheal in origin. In view of the chronicity and course of the disease, we advised that the patient be treated surgically.

One month later (in November, 1926), the operation was performed at the Hospital for Women of Maryland. The cervix was first thoroughly cauterized. The abdominal operation was performed through a midline suprapubic incision.

The omentum was so densely adherent to the anterior abdominal wall that the peritoneum had to be opened just below the umbilicus. The pelvic organs were completely covered by the thick, heavy omentum. The sigmoid was densely adherent over the left adnexae, which could not be seen but could be felt deep in the pelvis. The right adnexae were also adherent. The uterus contained a small fibroid tumor about as large as a marble.

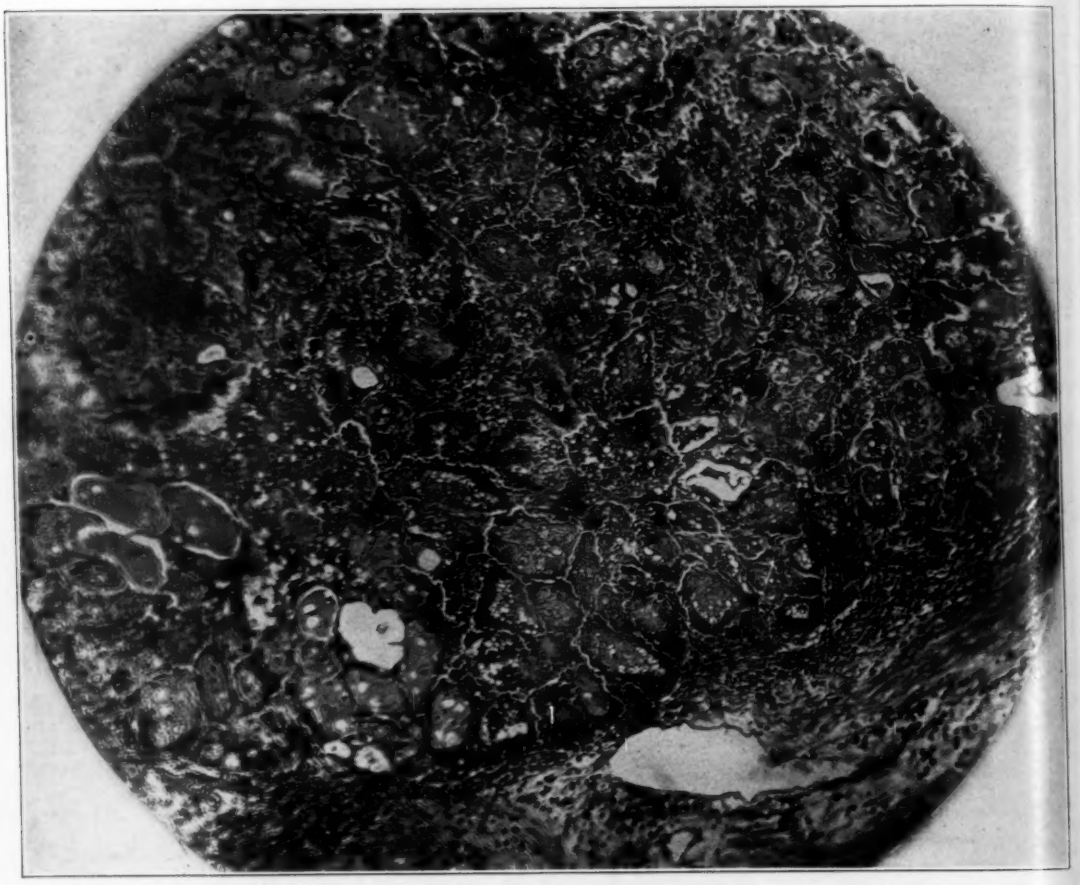

Fig. 6 (no. 31798).—Left tube showing alveolar carcinoma with marked lymphocytic infiltration and no invasion of tube wall.

The right ovary was riddled by small cysts; the right tube was closed. The left tube had the appearance of a fairly large hydrosalpinx, and under it one could feel the ovary, both fixed to the uterus and pelvic floor. While the left tube was being liberated, it ruptured, and a small papillary growth about 3 or 4 mm. in diameter popped out of it. It was firm, friable and grayish-white. With it escaped about 30 cc. of dark, serosanguineous fluid. We immediately gained the impression that

we were dealing with a carcinoma of the left ovary and decided to remove both tubes, ovaries and the supravaginal portion of the uterus. This was promptly done without accident.

There were no abdominal metastases or free fluid, and the pelvic glands were not enlarged. The convalescence was uneventful.

Fig. 7 (no. 31798).—Carcinomatous tumor nodule expressed from lumen of left tube during operative manipulation. It was attached by a slender pedicle; × 8.

We have seen this patient at intervals of about two months since the operation, and she has remained in perfect health, has gained in weight and has no discomfort. For a year after the operation, however, there was a good deal of pelvic induration which caused us some concern. Since it gradually was absorbed, we

decided that it was not a local recurrence, although we expected one. We sent the patient to Dr. Howard A. Kelly's sanatorium for radium treatment, but this was not given because of the continual improvement in the general health and the steady diminution in the pelvic induration. At the time this paper was written, more than two years after the operation, the patient enjoyed perfect health.

Gross Pathologic Examination.—The tissue included the supracervical portion of the uterus, both tubes and both ovaries. The uterus contained a small myoma,

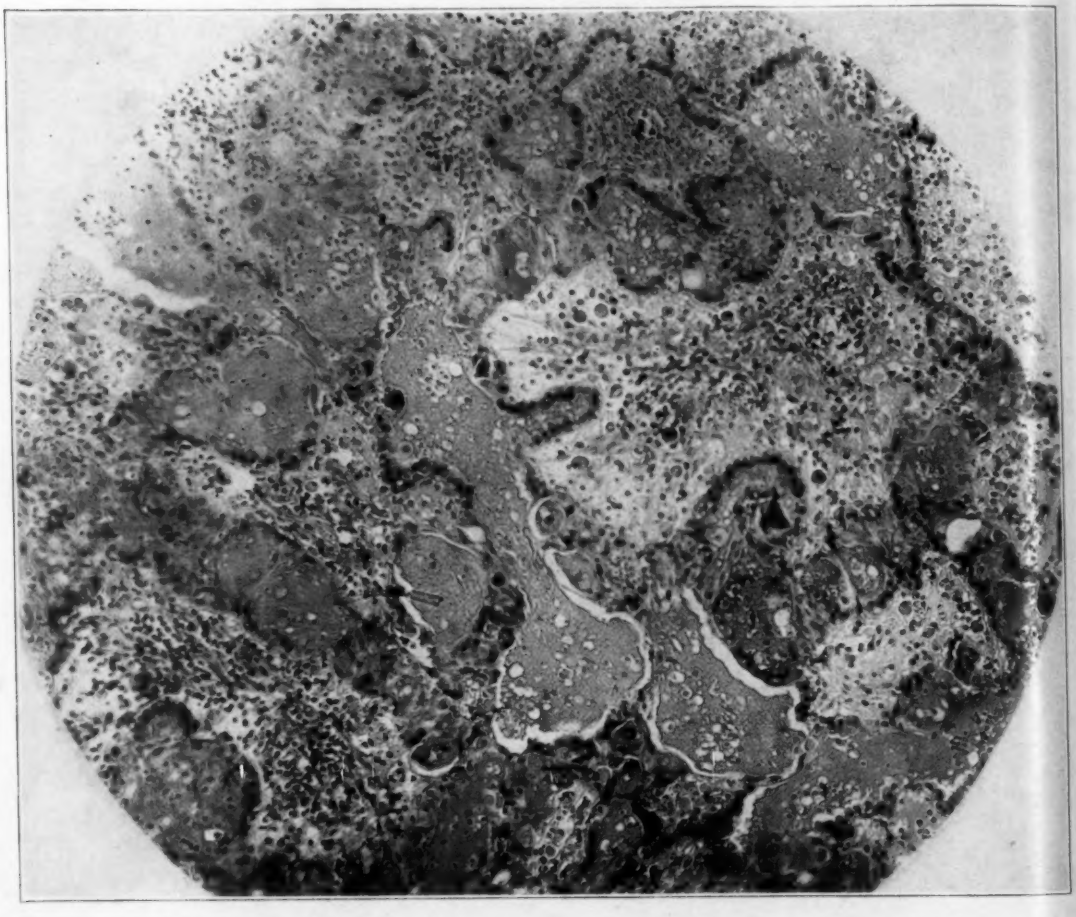

Fig. 8 (no. 31798).—Higher power view of tumor nodule shown in fig. 7, showing the alveolar carcinoma, delicate stroma, poorly differentiated papillae, and occasional mitotic figure.

about 2 cm. in diameter. The peritoneal surfaces were smooth, except for the raw areas caused by the adhesions and surgical dissection. No superficial metastases were evident.

The left tube was shaped like a retort; it had been opened, but still contained dark brown sanguineous fluid; numerous bits of tumor tissue flowed from the tube when it was opened further. The distal portion of the tube was hard and felt

solid. The fimbriated extremity was closed. The left ovary lay underneath and was adherent to the tube. The fimbriated extremity of the right tube was also closed. The right ovary was cystic and adherent to the right tube.

The uterine muscle was normal. The endometrium everywhere was smooth and pale.

Microscopic Pathologic Examination.—Left tube and ovary: Sections through the mass in the left tube showed that the tubal lumen was filled with a papillary growth, which was entirely limited to the tube and at no point had invaded the muscular wall. The mesosalpinx and ovary were normal. Under higher magnification, the tubal growth presented various pictures. The large papillary mass was frankly malignant, solid nests of carcinoma cells which presented marked variation in the size of the cells and nuclei being present. In general, the growth presented papillary and alveolar characteristics throughout. The tissue was studded with leukocytes and lymphocytes (figs. 6 and 8). The arrangement of the alveoli, the character of the cells, the variation in the size of the nuclei, their staining characteristics and mitotic figures stamped this growth as outspokenly malignant.

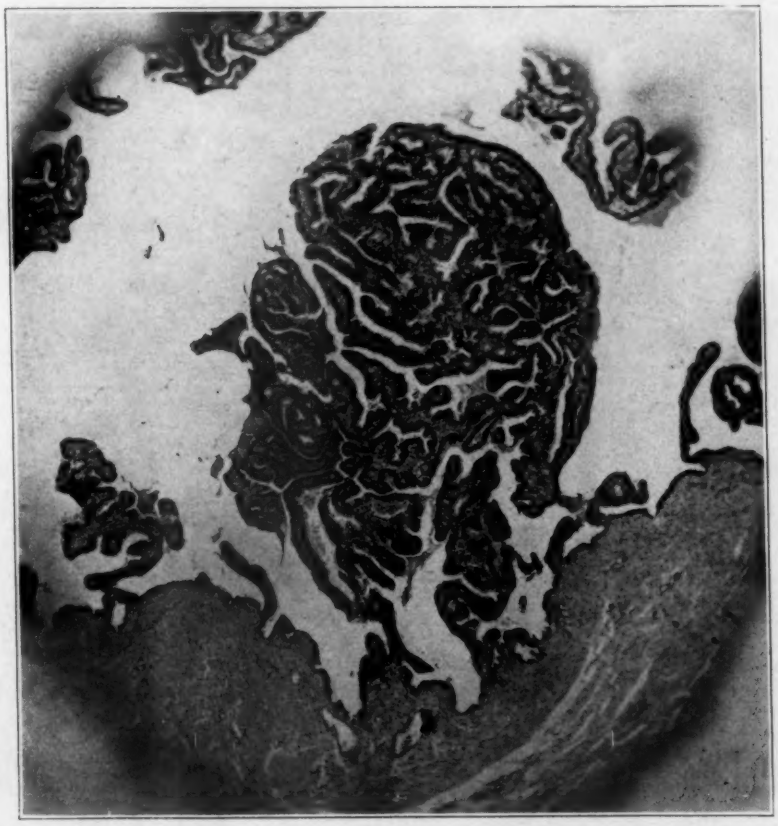

Fig. 9 (no. 31798).—Papilloma in right tube, which is frankly benign. Compare with fig. 5, which shows a malignant papilloma in the left tube.

In other areas, the papillary tumors showed every gradation from the frankly malignant picture previously described to epithelial and glandular hyperplasia with little cytologic evidence of malignant disease. Some of these epithelial tufts varied from normal tubal papillae only in their greater size and the dense pattern of the growth. In the normal papilla the core of connective tissue formed the bulk of the tuft; in these hyperplastic growths, the connective tissue was scant and the epithelium dense, crowding out the stroma and destroying all resemblance to the simple structure from which it originated (fig. 5). In some of these tufts,

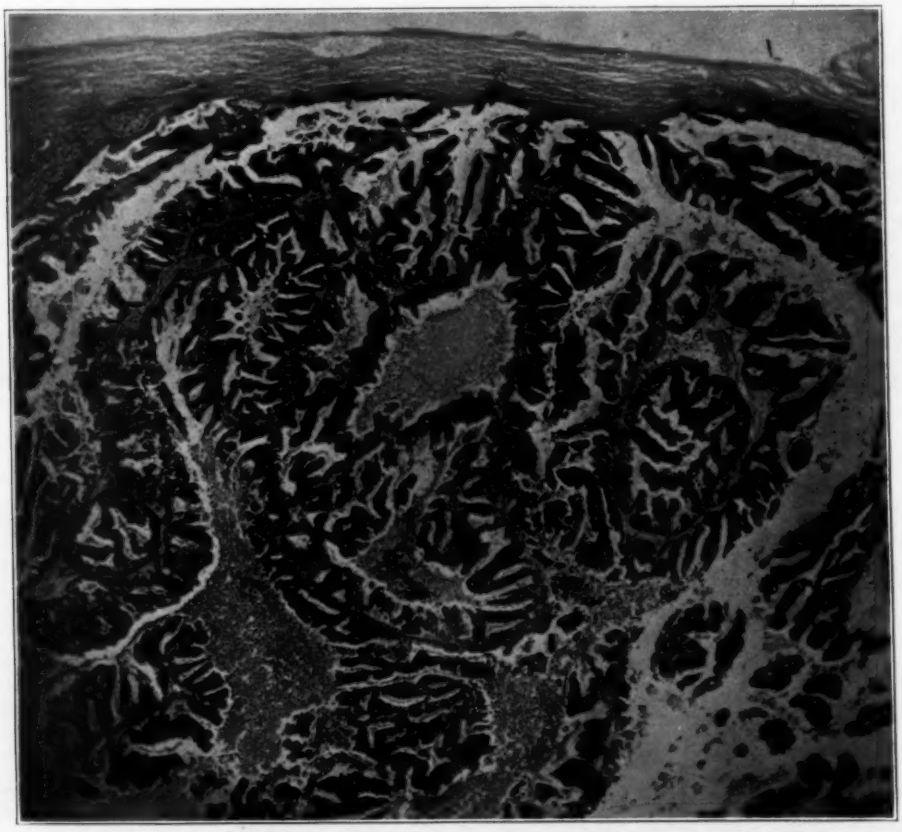

Fig. 10 (no. 29690).—The papillary type of growth, without invasion of the tubal wall, should be noted. Fimbriated extremity open. Recurrence and death in two months.

there were no mitotic figures, no significant variations in the size or staining characteristics of the nuclei and little heaping up of the epithelium. As in the case of adenocarcinoma of the body of the uterus, however, the pattern of the growth stamped it as a malignant process. In the same field, as in figure 5, one can find these adenomatous tufts, normal tubal papillae and outspoken islands of cancer side by side.

The right tube showed no active inflammation, the only evidence of salpingitis being the gross picture, the closed fimbriated extremity and adhesions. The

Summary of Fourteen Cases of Primary Tubal Carcinoma

Case	Age	Para.	Miscarriages	Symptoms	Preoperative Diagnosis	Operative Observations and Diagnosis	Operation	End-Result
1009	48	1	0	Menorrhagia; abdominal tumor	Myoma.....	Large uterine myoma; tubal carcinoma not suspected	Hysterectomy; bilateral salpingo-oophorectomy	Died in 5 months; peritoneal recurrence
2376*	63	4	0	Bloody vaginal discharge; fever 8 months	Pyosalpinx.....	Tubal mass like pyosalpinx; carcinoma not suspected	Hysterectomy; bilateral salpingectomy; left oophorectomy, 1898	Recurrence in 1900; operation; well, 1902
5919	53	4	0	Pain in left side; watery, bloody, vaginal discharge	Retroflexed uterus; salpingitis	Tube freely movable, vascular; few adhesions	(1) Left salpingo-oophorectomy; (2) curettage, two weeks later	Died, recurrence, 4 years
7697†	58	1	0	Abdominal tumor; dyspnea	Large ovarian cyst.....	Ovarian cyst; tubal cancer not suspected	Left salpingo-oophorectomy	Lived 5 years; cause of death not known
8114‡	55	3	0	Bloody vaginal discharge; pain on defecation; pelvic pain	Myoma.....	Metastases in omentum; extension to rectum	Panhysterectomy; bilateral salpingo-oophorectomy; resection of rectum	Died, 6 months
11536‡	46	0	1	Bloody vaginal discharge; abdominal mass; pain; leukorrhea	Pyosalpinx.....	Small uterus; enormous bilateral tubal cancer (figs. 2 and 3)	Hysterectomy; bilateral salpingo-oophorectomy	Recurrence in 3½ years
18155	47	0	0	Loss of weight; weakness	?.....	Ovarian cancer; appendix bound in tubo-ovarian mass; removed in toto	Appendectomy; right salpingo-oophorectomy	Recurrence and death in 13 months
18568†	44	7	0	Abdominal pain; leukorrhea; dysuria	Myomata uteri; chronic salpingitis	Omental metastases; small myoma; chronic salpingitis	Hysterectomy; double salpingo-oophorectomy	Died 6 months later
19087†	47	0	0	Abdominal swelling; vomiting	Myoma; ovarian cancer	Clear fluid; peritoneal metastases; tubes open	Left salpingectomy	Died, 1 year
19557	47	4	1	Abdominal pain	Chronic salpingitis.....	Hydrosalpinx, left; degenerating mass in right tube, densely adherent	Panhysterectomy; bilateral salpingo-oophorectomy	Died, 7 days; hemorrhage
29690	46	0	0	Abdominal enlargement; pain	Pelvic tumor ?.....	Carcinoma of pelvis, source undetermined	Partial removal	Died, 2 months
31088†	43	3	12	Bloody vaginal discharge; abdominal tumor	Chronic salpingitis; cancer ?	Chronic salpingitis	(1) Curettage, 1925; (2) curettage, hysterectomy; bilateral salpingo-oophorectomy, 1923	Well, 1 year
31798	29	0	0	Pelvic pain; leukorrhea	Chronic salpingitis.....	Chronic salpingitis; ovarian cancer	Hysterectomy; double salpingo-oophorectomy, 1926	Well, 1929
34144	52	0	0	Bloody vaginal discharge	Cancer of body of uterus	Small mass in tube; metastasis in endometrium	Curettage; hysterectomy; left salpingectomy, 1928	Well, 1929

* Reported by Hurdon (footnote 1).
† Reported by Vest (footnote 2).
‡ Reported by Cullen (footnote 3).

epithelium was normal almost everywhere. In one area, a definite papillary growth about 3 mm. in diameter (fig. 9) was found. It showed the same hyperplastic characteristics as similar growths in the left tube (fig. 10). There was a definite tendency toward heaping up of the epithelium; the alveolar pattern was dense, the connective tissue scant and compressed by the epithelial overgrowth. The individual cells showed no evidence of malignant disease, but the pattern was abnormal. In view of the condition found in the opposite tube, this adenomatous hyperplasia becomes particularly significant and forces us to the conclusion that it may represent the first step of the malignant process which was fully developed in the other fallopian tube.

Except for small graafian follicle cysts, the right ovary was normal. The myometrium and endometrium of the uterus were everywhere normal. The myoma showed no unusual characteristics.

Pathologic Diagnosis.—A diagnosis was made of primary carcinoma of the left tube; epithelial hyperplasia of the right tube; normal ovaries and normal endometrium; myoma of the uterus; chronic salpingitis.

SUMMARY

Primary carcinoma of the fallopian tube is one of the rarest of gynecologic diseases. It presents the usual incidence in regard to age. There seem to be no definite predisposing factors. The earliest and most constant symptoms are sharp, lancinating pelvic pain, associated with vaginal discharge which may at times be blood-tinged. Menstrual disturbances occasionally occur. The physical manifestations are variable. The diagnosis is extremely difficult, having been suspected in only one of more than 200 cases before operation. The treatment should be early removal of the uterus and of both tubes and both ovaries. The results of past treatment have been highly unsatisfactory. It is to be hoped that the results will be improved by earlier intervention and more complete extirpation. The malignant nature of the disease can usually be readily determined on the operating table by the routine macroscopic examination of tissues immediately after their removal.

LEUKOPLAKIA OF THE RENAL PELVIS*

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

Leukoplakia of the renal pelvis has been of increasing interest as indicated by its recognition in recent years. It is of interest to the pathologist because of its unknown pathogenesis and of clinical importance to the urologist for the diagnostic and therapeutic difficulties. It is a paradox, simulating an epithelial process (ectoderm) and yet occurring on the mucous membranes of the urinary tract, a structure of mesodermal and entodermal origin. The unsatisfactory treatment for leukoplakia, as well as the possibility of malignant degeneration, makes the condition one of clinical importance.

Leukoplakia of the renal pelvis occurs more frequently than is thought. Its infrequent occurrence is more apparent than real, the condition being overlooked through a laxity in observation of genito-urinary disease. Up to the present, sixty-seven proved cases have been recorded, inclusive of the case herein reported. Of the sixty-seven cases, forty-two were recorded prior to 1923, and twenty-five cases since, indicating that the condition is being recognized more frequently by all observers. While the observations are chiefly European, leukoplakia of the urinary tract has been increasingly recognized in recent years by American observers. Rokitansky, in 1861, first mentioned leukoplakia in the bladder, and Ebstein, in 1882, described the first case of leukoplakia in the kidney. Cabot, in 1891, and Beer, in 1914, observed the first cases in the bladder and kidney, respectively, on this continent.

Because of the unknown etiology, important in the diagnosis, treatment and association with a malignant condition, it is essential to collect additional data and to stimulate an increasing recognition of leukoplakia of the renal pelvis.

REPORT OF A CASE

History.—A Mexican housewife, aged 26, was referred by Dr. L. C. Audrain with the complaint of marked frequency of and burning on urination, soreness across the lower part of the abdomen and pain in the left lumbar region. The family history was irrelevant. The patient gave a history of measles, chickenpox and smallpox. She said that she had never had any venereal disease. The menstrual history was normal. There had been seven full-term pregnancies, with no miscarriages. The habits of the patient were good.

The condition began with pain in the left lumbar region and frequency of urination three years before Dr. Audrain saw the patient. Four months before, the patient developed tenderness across the lower part of the abdomen, with burn-

* Submitted for publication, May 24, 1929.

ing on urination and malaise. At the time of examination, she had marked frequency of urination, bordering on incontinence. The pains in the left lumbar region and lower part of the abdomen had increased in intensity. There seemed to be a sense of difficult urination with severe attacks of burning and occasionally a slight hematuria. There had been a marked loss in weight, but the patient did not know how much.

The physical examination showed an emaciated, sick-appearing woman, lying in bed and apparently in distress. The temperature was 99 F., the pulse rate 84, the respiratory rate 22 and the weight 97 pounds (44 Kg.). There was marked tenderness in the left lumbar region; this extended anteriorly and downward. The remainder of the physical examination was negative.

Examination of the blood showed hemoglobin, 65 per cent; red blood cells, 3,810,000; white blood cells, 11,400; polymorphonuclears, 74 per cent; small lymphocytes, 18 per cent; large lymphocytes, 4 per cent and large mononuclears, 2 per cent. Examination of the urine showed: extreme cloudiness; specific gravity, 1.018; light straw color; p_H, 7.2; a heavy trace of albumin and no sugar. Microscopic examination disclosed numerous pus and red blood cells, and few epithelial cells. There were no casts. Phenolsulphonphthalein injected intramuscularly appeared in the urine as follows: 50 per cent in the first hour and 15 per cent in the second hour, a total of 65 per cent. The Wassermann reaction of the blood was negative.

On cystoscopic examination, the wall of the bladder showed a severe and diffuse cystitis; the capacity of the bladder was 30 cc. The vesical neck had a marked bullous edema. The right ureteral orifice was normal; there was marked ulceration around the left orifice. Both ureters were easily catheterized to the kidneys. The urine from the right kidney contained numerous red blood cells and an occasional white blood cell; there were no epithelial cells, no casts and no organisms. The urine of the left kidney was cloudy and tinged with blood. Microscopic study revealed numerous blood and pus cells and gram-positive cocci. The urine of the bladder showed a similar picture. No tubercle bacilli were found in any of the specimens. All cultures failed to grow although staphylococci were the predominating organisms in the stained smears. Phenolsulphonphthalein, injected intravenously, appeared in three and one half minutes on the right side and returned 32 per cent of the dye in thirty minutes. The time of appearance in the left kidney was five minutes, with 14 per cent secreted in thirty minutes. There was no leakage from the bladder. Pyelographic studies showed a left pyonephrosis (fig. 1).

The diagnosis was left pyonephrosis with cystitis and a contracted bladder.

Because of the patient's marked anemia, a blood transfusion was given two days before the operation. A left nephrectomy was performed under ethylene oxygen anesthesia. Convalescence was uneventful except for an infection of the wound, which cleared up readily under daily irrigations with surgical solution of chlorinated soda (Dakin's solution).

When the patient was seen, six months later (Dec. 1, 1927), she had gained 20 pounds (9 Kg.) in weight, felt well and was able to do her housework. Nocturia occurred twice and diuria every two or three hours. The remaining signs and symptoms had cleared up entirely. She did not return for further observation of the bladder.

The specimen consisted of a left kidney weighing 190 Gm. The surface was very rough, a mottled purplish pink, and irregular. On section six irregular cavities were seen which were connected with each other and with the pelvis. The pelvis and cavity-like calices were covered by a whitish, wrinkled, thick, parch-

ment-like membrane (fig. 2). The remainder of the renal parenchyma showed little differentiation and was swollen in appearance. The capsule stripped with difficulty; a coarsely scarred surface remained.

Microscopic Examination.—Many areas of the kidney had been replaced by inflammatory products composed of small round cells, eosinophils and some leukocytes and connective tissue, in certain areas approximating abscess formation. The adjacent tissue of the kidney showed edema and cloudy swelling. The tubules appeared to be slightly dilated, as did some of the glomeruli, while others were sclerosed and congested. The blood vessels showed marked fibrosis. Everywhere the interstitial connective tissue was increased (fig. 5).

Fig. 1.—Left pyelogram (20 per cent colloidal silver iodide compound), showing the picture of a typical pyonephrosis.

Examination of the pelvic mucosa showed a definite metamorphosis into squamous epithelium similar to the skin. There was a marked chronic inflammatory reaction, chiefly of small round cells, beneath this process and in some areas infiltrating it. The squamous epithelium showed a cornified layer beneath which was a granular layer of cells (keratohyaline granules). Underneath could be seen a well defined basal layer. Some sections showed a tendency toward papillary downgrowth of this layer. The entire picture was that of a well defined leukoplakia (figs. 3 and 4).

The final diagnosis was chronic pyonephrosis with pelvic leukoplakia.

COMMENT

This case definitely demonstrated a leukoplakia which appeared to be limited to the renal pelvis and calices. It was associated with or complicated by an infection of long duration, a severe pyonephrosis which had practically destroyed the kidney. In all respects, this case definitely simulated the various cases of leukoplakia reported in the literature. In accord with the present theories of leukoplakial pathogenesis, it may be considered as associated with or due to the severe chronic infection of the urinary tract.

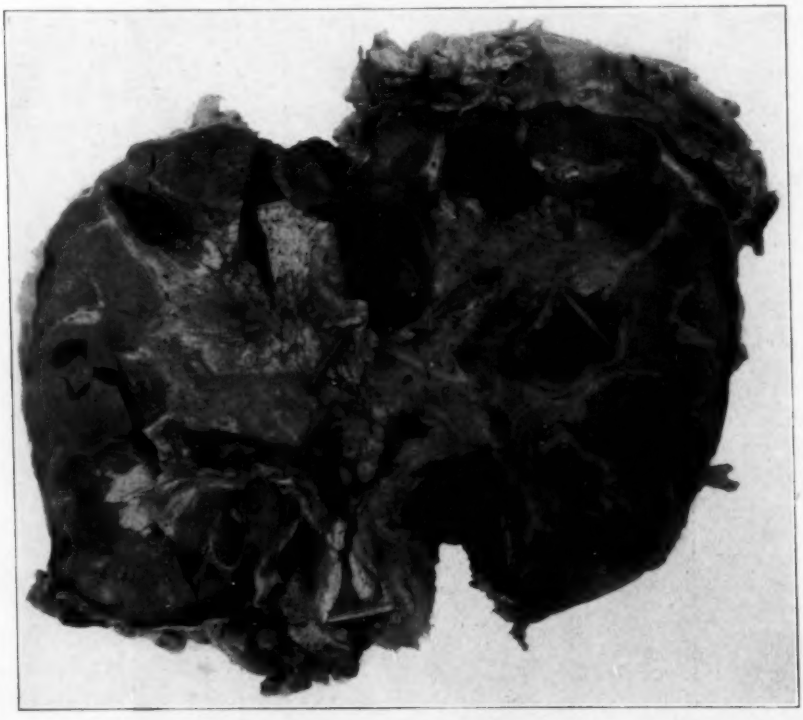

Fig. 2.—Sagittally sectioned kidney of reported case, showing the white skin-like areas covering most of the pelvis and calices and extending in patchlike formation to the ureteropelvic junction. The pelvic wall and ureter show marked thickening. The calices present the picture of a pyonephrosis.

PATHOLOGIC ANATOMY

The occurrence of cornified squamous epithelium on the mucous membranes of the body has always engrossed the interest of observers. Distributed throughout the various parts of the body, it has been named leukoplakia, metaplasia, prosoplasia, epithelmetaplasia, pachydermia, xerosis, cholesteatoma, leukoplasia, psoriasis membranae

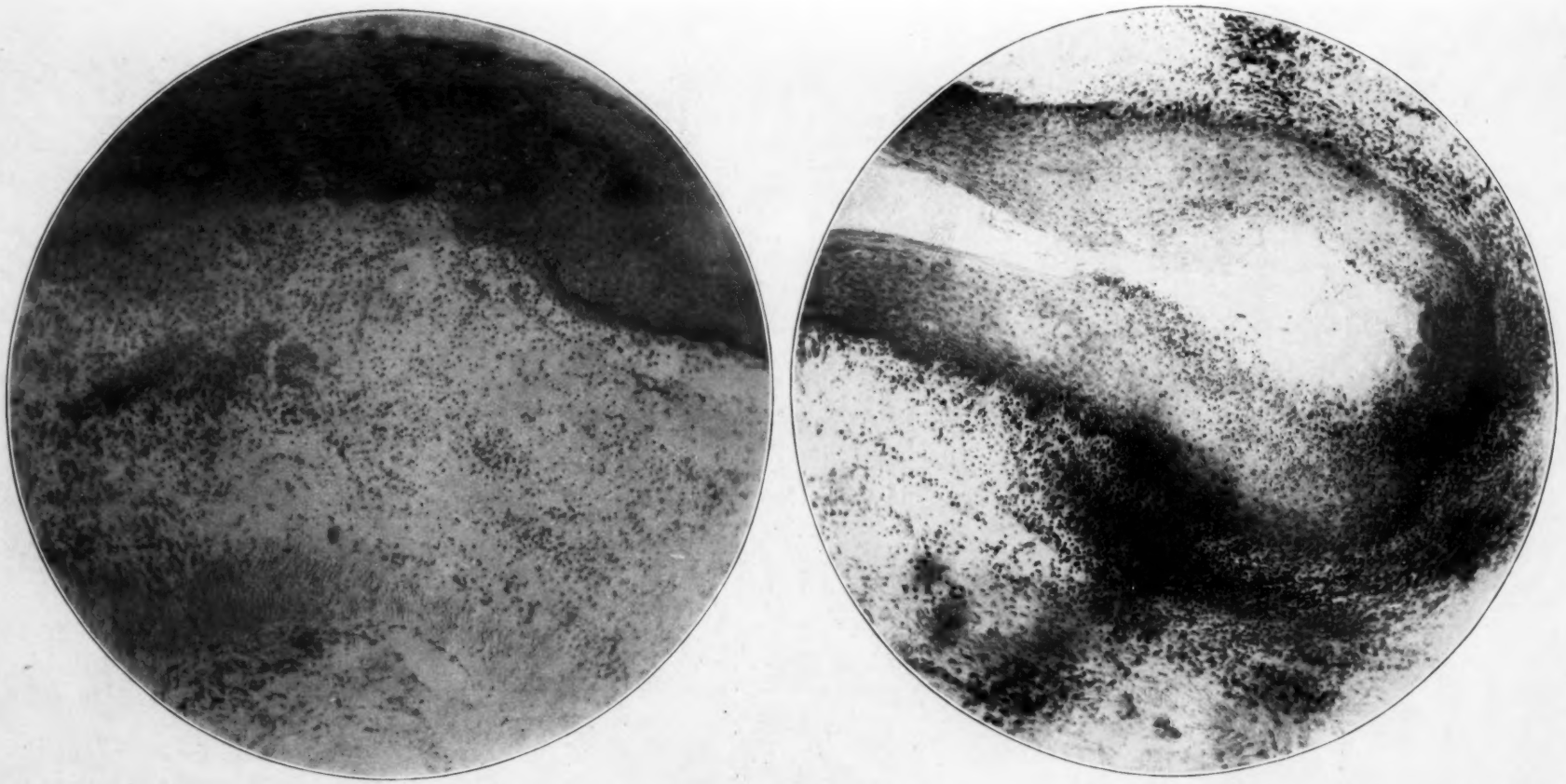

Fig. 3.—Low power photomicrograph, showing the extensive epidermization of the renal pelvic mucous membrane. Note the marked resemblance to skin. The lymphocytic infiltration is heavy in some areas bordering on abscess formation. Some parts of the leukoplakic membrane show infiltration with inflammatory cellular elements.

mucosae, leukokeratosis, tylosis and epidermal plaques. It has been found on the mucous membranes of the tongue, mouth, gums, esophagus, gallbladder, rectum, nose, frontal sinuses, ear-drums, vagina, uterus and the urinary tract.

The morphology of leukoplakia is described uniformly by nearly all observers. As the term signifies, leukoplakia refers to the formation of white patches on mucous membranes, although it may also include

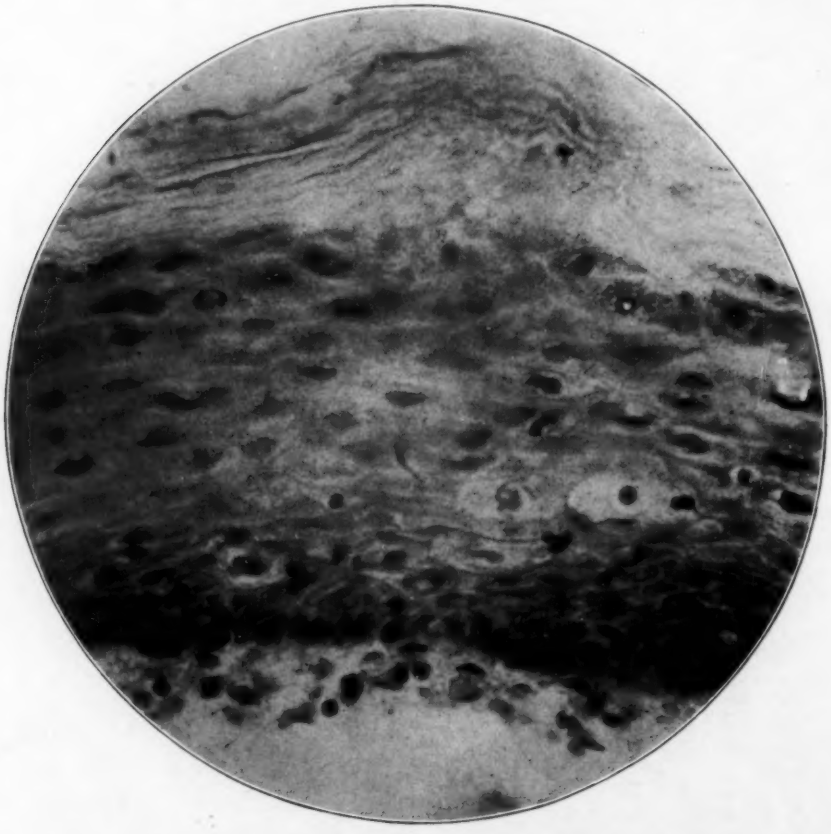

Fig. 4.—High power photomicrograph, showing the epidermization process of the pelvic mucosa with the keratohyaline granulation of the stratum granulosum well defined beneath the lamellated desquamating layer.

those forms found on the surface of the skin and described as a xeroderma or keratosis. Pathologically defined, it consists essentially of a thickening or keratinization of epithelium taking on a definite epidermoid character, regardless of location in the body. In the pelvis of the kidney there can be found well defined skinlike membranes, whitish or grayish, pearly or silvery, with a surface in fine or coarse

folds. Usually the pelvis is covered with areas ranging from a very small to a large size and in some instances lining the entire pelvis. This leukoplakial membrane is dense and resistant and often can be dislodged with difficulty. The denuded underlying tissues will then show a papillary surface.

Microscopically, the leukoplakial membranes bear a definite resemblance to skin, presenting the characteristic layers of the stratum

Fig. 5.—Destruction of the renal parenchyma. Note the marked increase of fibrous tissue interstitially, and the vascular sclerosis; the damaged glomeruli and marked lymphocytic infiltration border on abscess formation.

germinatum, mucosum, granulosum lucidum and corneum. The granular layer shows the typical keratohyaline granules seen in the skin, and the cells of the rete show the typical intercellular bridges. A marked lymphocytic infiltration of the underlying connective tissues due to the accompanying inflammatory conditions is present.

Some observers have attempted to differentiate two types of epithelium. The first type mentioned by Lavonius, Ikeda, Hallé and

Englisch is similar to the epidermis. There is seen a single row of cylindric basal cells topped by the prickle cell layer, with the keratohyaline granular layer next and the cornified layer on top. The epithelium differs, however, from the true epidermis in that the structure is irregular and the thickness of the layers is variable, as mentioned by Englisch. Furthermore, Hallé has shown that the epithelium of leukoplakia possesses a stronger power of growth which manifests itself in a double tendency, on the one side to a proliferation of the deep layers noted by Francke in his cases and thought by Englisch to be rare, and on the other, to a marked desquamation of the upper cornified layer. This might result in a filling of the urinary tract with cholesteatomatous material. According to Karo, leukoplakia and cholesteatoma are not the same, their origin only being common, with leukoplakia as the primary disease. The latter leads to the shedding of wide, cornified, epithelial fragments which may collect into a tumor-like, pearly, onion peel-like, stratified epithelial mass, generally termed "cholesteatoma," and later cause an obstruction in the urinary tract. "Cholesteatoma," according to Corsdress, is a misleading term since there is no true formation of tumor in a pathologic sense. According to the researches of Schridde, it is designated as early leukoplakia, without cornification, as differentiated from true leukoplakia, which is characterized by a true cornification of the epithelium.

A still further differentiation from epidermis is that the cornification is not completely developed. The cornified layer stains with the Gram as with the Gram-Weigert stain (Ernest), while it will not retain the golden orange when tested according to the method of Ebbringhaus. Lavonius observed in this type still another difference in that a layer of flattened cells without granules and nuclei lies above the lamellated layer.

In the second type, over the lowermost layer of prickle-cells there lie several rows of polygonal, less flattened cells with round or comma-shaped nuclei and with a lightly-staining protoplasm. The cornified and eleiden layers are frequently missing. There are present only a few cells of the keratohyaline layer. This type corresponds to the so-called third type of Hallé and to the second type of Ikeda and Lavonius. The second type of Hallé and Englisch, in which the cornified layer lies on a few rows of basal cells, does not appear to be frequent.

The type of epithelium described by Stoerck and Lichtenstern in which the upper cell layers simulate nucleated scales, while the lower cells cannot be differentiated from the ordinary transitional epithelium, approaches a third type of Ikeda and simulates the beginning stage of the others, yet does not belong to leukoplakia. The epidermis-like character of the superficial layers, as well as the characteristic single

basal cell layer with several prickle-cell layers overlying, cannot be separated from the picture of leukoplakia.

Pathogenesis.—The occurrence of leukoplakia in the urinary tract presents a paradox in that one finds an ectodermal type of structure occurring in organs of mesodermal and entodermal origin. This has been the subject for many theories. The condition has been noted in many parts of the body, Virchow describing it as pachydermia laryngis and von Graefe as xerosis of the conjunctiva; Schönemann noted the occurrence of cornified squamous epithelium in ozena of the nose, while Zeller and R. Meyer found it in the uterus, and Deetz in the gallbladder. Rokitansky, in 1861, was the first to describe leukoplakia in the urinary tract when he noted that "in the inflamed bladder there occurs occasionally an epidermoid production, at times circumscribed, at other times occupying the whole mucosa of the urinary apparatus; it produces an abundant desquamation of thick scales, stratified, white, shiny, in the form of cellular epidermoid plates; the adjacent mucosa is chonically inflamed and villous."

Various observers have sought to explain the leukoplakic process on the basis of some disease. Many years ago, Hunter and Babington, and later Schwimmer, noted that the epidermization of mucous membranes was not necessarily due to syphilis. Syphilis, while discarded, recently received support from S. and E. Li Virghi. Tuberculosis, found as an associated condition by some observers, has been accorded some consideration from Beselin and the Nordique-Lavonius school. Such theories as that of substitution, in which the epidermization was thought to extend into the urinary tract through some fistulous opening, has long been discarded. This was originally advanced by Eicholz, Posner and Marchand. Marchand later supported the theory of metaplasia.

The congenital theory and the theory of cell rests (Keimversprengung) have had many advocates. Lecène, in promulgating this theory, noted that there might be an arrest of development of the urinary tract by what he called an epidermoidal heteropia. The wolffian body, from which the ureter and pelvis are developed, shows a complex development, and since at some time there may be an intimate relationship with the ectoderm, ectodermal cells may be included. Studies on embryos have shown that during a certain time the excretory canal of the pronephros is included in the ectoderm. Staehlin, R. Meyer, Guinard and others stated that the pronephric portion of the wolffian body is of ectodermal origin and that the embryogeny of the urogenital system may be complicated by such misplaced cells from the primitive ectodermal layer and give rise to the growth of these aberrant cell rests subsequently found in the genito-urinary tract. It has been found that there may be pavement epithelium in the urinary tract.

Lavonius examined 150 renal pelves according to the method of Zilliakus, and microscopically demonstrated five cases in which leukoplakia might originate. A case was observed by Leber in a girl, aged 4 months, with xanthoma of both conjunctivae together with proliferation of the epithelium of the pelvis.

Not infrequently small areas occur in the urinary bladder in which the epithelium shows cornification. Lubarsch, in 160 autopsies, found six cases with islands of leukoplakia, while Heymann noted small circumscribed areas of cornification in ten of twenty cases. Ribbert and Albarran held that these islands of flattened epithelium were of embryonal origin and later underwent leukoplakial degeneration. Ribbert pointed out that these cells which may appear normal in this location nevertheless possessed embryonic potentialities and that some of these cells were partially differentiated and could undergo changes more readily; moreover, that the newly developed cells were not as highly specialized as the preexisting cells and that the leukoplakial change might occur only in the presence of certain abnormal conditions. Zeller, in his work, showed many cases with pavement epithelium in the uterus to which he attributed an etiologic rôle in the cause and continuation of endometritis. From the evidence submitted, the congenital theory and the theory of cell rests are not sufficient to explain the transformation of the cylindric epithelium into flat epithelium. The universal association with a long-standing infection is left unexplained, unless it were accepted that leukoplakia invited infection, but clinical data hardly substantiate this theory.

The theory of metaplasia, supported by many authors, has lent itself best to the explanation of most cases. The idea of metaplasia which originally had a loose meaning has in the course of time assumed a more specific aspect. At present, only a process in which the new epithelium does not develop from the original anlage is designated as a metaplasia of the epithelium. In some cases in which cornified squamous epithelium is found on a mucous membrane where transitional epithelium originally is normal, it has been conceived that there might have been an abnormally continued development of the transitional epithelium, termed by Schridde as "prosoplasia." This was also known as an "indirect metaplasia" in contrast to Virchow's view in which he defined metaplasia as a "direct change of one cell into another cell which was architecturally different but had not completely given up its characteristic structure." In the light of present knowledge of metaplasia, Orth has more accurately defined it as the transformation of a well characterized tissue into another tissue that is equally well defined but morphologically and functionally different.

Haythorn especially dwelt on metaplasia in accounting for the epidermoid changes in the bronchi. His studies as well as those in

recent years by Francke, Allemann, Karo, and Hinman and Gibson have been increasingly supported by observers until now it is the most widely accepted theory. Haythorn's theory in reality supports the older views of Schridde so far as he considers the metaplastic cells as newly formed cells and that they come from the growing layer. Ribbert's view also is supported in that the newly formed cells are less highly specialized than the normal cells, and that the changes in the surrounding tissue have a strong influence on the type of new cells formed. Since all cases are associated with long-standing chronic infection, it is thought that the mucosa is destroyed by a progressive process. The damage may be profound and exhausting and may include the basement membrane. Being unable to regenerate their own type, the cells bring forth a more protective cornified type. The mucosa in its exhausted condition and beyond specific regeneration seeks to protect itself with the best type of reparative cell it can produce. There is also probably a link between the injury to the basement membrane and tumor growth, and hence the irritants and inflammation which destroy them open the way for metaplasia and new growth. The process involving the basement membrane therefore favors metaplasia. By this type of hyperplasia, the loss is covered and a new cell with apparently increased resistance appears. This active defense is assumed to occur in the comparatively mild infections and irritations acting over a longer period; if the irritating factors are more intense, an excessive hyperplasia may occur, breaking through the borders and developing into a malignant condition. The desquamated cells have been found to contain glycogen. Even the most rudimentary types of metaplasia contain it, and it is entirely lacking in the normal epithelium (Schiele, Gierke and Ikeda).

Küttner and Klug considered leukoplakia on the basis of tumor formation. Corsdress differed from this opinion, considering cholesteatoma as not being a real tumor since there is no multiplication of cellular substance characteristic of tumors, but only a transformation of the character of the cells.

Leukoplakia has been considered as an irritative lesion, on the basis of bacterial toxins, similar to malakoplakia, cystitis cystica, trigonitis granulosa, polyposis of the vesical neck and venereal condylomas. Briggs and Maxwell, and Kretschmer analyzed the bacteriology of collected cases, but were unable to reach any conclusion. Leber believed that there must be some specific bacterial irritant to cause the cornification, since he found the same type of bacteria on the leukoplakia of the renal pelvis as on the xerosis of the conjunctiva. In support of this fact, Kuschbert and Neisser designated a xerobacillus as the cause, although its harmlessness was later demonstrated by

Schreiber and Neisser. It is possible for leukoplakia to occur without the presence of microbian infection, as was demonstrated by Escat in his cases of tumors of the bladder on a leukoplakic basis.

Many questions still remain to be solved. While it is assumed by most observers that leukoplakia is caused by a chronic irritation, whether inflammatory, chemical or mechanical, why are there so comparatively few cases of leukoplakia in comparison to the numerous cases of pyonephrosis, hydronephrosis or nephrolithiasis? Granting the process to be a metaplastic one in epithelial changes, why does a leukoplakia occur on one occasion and pyelitis cystica on another? When the leukoplakia has become a fully developed process, why are there well defined areas of it, while the adjacent epithelium exposed to the same pathologic influences remains unchanged? Finally, since there is a cornification which has been explained by Recktenwald, Hinman and others as a protective measure against destructive irritation, why should such a process proceed to a more pathologic condition such as carcinoma?

Relation to Malignant Disease.—The evidence is slowly increasing that leukoplakia may be the forerunner of the squamous cell carcinoma (Hinman and Gibson, Scholl, Kretschmer, von Borza and Patch). An analysis of the sixty-seven collected cases of leukoplakia of the kidney has revealed seven squamous cell carcinomas and one adenocarcinoma, an incidence of 11.9 per cent. Of these, six occurred in the renal pelvis (Kischensky, Spiess, Aschner, Thomson-Walker, Patch and Fuetterer [adenocarcinoma]) and two in the bladder (Rona and Recktenwald). Patch, in a recent review of the literature, found 152 cases of squamous cell carcinoma in the urinary tract—36 renal, 6 ureteral and 110 vesical cases—showing that this type of malignant disease is not rare. A further analysis revealed thirteen cases in the kidney and bladder which had leukoplakia and squamous cell carcinoma coexisting. These figures show a greater occurrence of these conditions than is surmised by many observers. Added significance should therefore be given to Hinman and Gibson's theory that leukoplakia is the forerunner of the squamous cell carcinoma. Leukoplakia, while being a physiologico-metaplastic process, may therefore become a pathologic one in some cases. Its presence alone would tend to maintain an incurable state of chronic inflammation and irritation. The latter maintain a continuous activity of epithelial proliferation as a protective process. Should this proliferative activity and destruction continue over a period of time, these cells may then show a malignant change. Just why a defensive process such as leukoplakia could be stimulated to undergo a malignant change is one of the weaknesses of this theory. Yet the evidence submitted from time to time is becoming more supportive. Patch recently demonstrated the transitional

stages in a case in which repeated examinations disclosed lesions of an intermediary type which, while not definitely malignant, were undoubtedly precancerous. Hinman, Kutzmann and Gibson demonstrated in one of their cases, although not so definitely, an early papillary downgrowth with a beginning break in the basement membrane suggestive of malignant disease, and therefore considered it as precancerous. Kretschmer has referred to leukoplakia, stone and chronic infection as the recognized forerunners of nonpapillary carcinoma of the renal pelvis.

Von Borza, in describing squamous cell carcinoma, considered not only local but also constitutional factors, such as the endocrine system. The hormones, being distributed as chemical irritants through the body,

Fig. 6.—An incipient stage of squamous cell metaplasia (leukoplakia) on the mucous membrane of a renal pelvis. There can be seen the normal transitional epithelium at the left, and the denuded epithelium and basement membrane on the right. Beneath these is a thick layer of granulation tissue infiltrated with lymphocytes. (Courtesy of Dr. Frank Hinman.)

have a specific action on the cells and tissues. He cited Biedl and Hertwig who stated that every organ, tissue and cell can be changed in its relationship by a change of one specific hormone to another. The toxins of the rapidly increasing cells lower the resistance and there is nothing to hinder local growth.

Wolbach, in conjunction with Howe, made some interesting pathologic observations in the deficiency diseases or the avitaminoses. In vitamin A deficiency, known as xerophthalmia or keratomalacia, a striking and extensively distributed epithelial metaplasia was found in

the conjunctivae, ocular glands, alimentary tract, respiratory tract and genito-urinary tract. It was noted that the epithelium was replaced by stratified keratinizing epithelium, strongly resembling leukoplakia. Wolbach found that a number of the experimental animals (rats) with this disease died of obstruction in the genito-urinary tract caused by its occlusion with desquamated keratinized epithelial cells.

Clinical Picture.—Symptomatically, leukoplakia of the renal pelvis per se presents nothing singular or characteristic. The outstanding points are the associated urinary infectious diseases and their chronicity. The leukoplakia itself is not discovered until operation or at autopsy, treatment being instituted for the associated condition.

Leukoplakia of the renal pelvis occurs more frequently than is thought, but has probably been overlooked through lax observation of pathologic conditions of the genito-urinary tract. A review of the literature reveals sixty-seven cases inclusive of the case herein given. The rarity of the condition seems to be only apparent. Patch noted that up to 1929, 123 cases had been reported in the entire urinary tract exclusive of the urethra.

Leukoplakia may occur in any portion of the urinary tract from the renal pelvis to the urethra. Stevens, Blum, Czerny and Bugbee even reported cases of diverticulum of the bladder containing leukoplakia. Briggs and Maxwell analyzing eighty cases in the urinary tract, including those reported and their own, found the following distribution: vesical forty, renal twenty-four, renal and ureteral ten, ureteral and vesical four, and renal or ureteral or both two. Since the division is almost equal—forty-four vesical and forty renal cases—they concluded that it must occur more frequently in the kidney, this diagnosis being made only at operation or necropsy, while the vesical cases might be more often diagnosed by cystoscopic observation of the bladder. Sixteen of the collected sixty-seven kidney cases had leukoplakia elsewhere: seven in the ureter, four in the entire urinary tract, two in the bladder, two in the ureter and bladder and one in the eye.

Leukoplakia of the renal pelvis may occur at any time during life, its greatest frequency, however, being in the fourth decade, the third and fifth decades following. The youngest patient reported was 4 months (Leber) and the oldest 70 years of age (Hallé) (fig. 7).

Leukoplakia of the renal pelvis occurs equally in both sexes. In the sixty-seven collected cases it was found in twenty-nine males and twenty-eight females, ten cases not being stated. This observation confirms an earlier report of Hinman, Kutzmann and Gibson and is at variance with Hennessey in whose recent review of seventy-five cases of leukoplakia throughout the urinary tract, fifty-six were in the male and nineteen in the female, a ratio of 3:1. Corsdress also found leukoplakia of the urinary tract in general to be more prevalent in males

in the ratio of almost 2:1. The latter observations, however, seem to be true of leukoplakia in the lower part of the urinary tract.

The distribution of the leukoplakia in the sixty-seven cases as to sides was right thirty-two, left seventeen, bilateral three and not stated fifteen. From this it may be noted that the condition tends to be unilateral, which is of importance in the treatment.

While there are some reported cases of uncomplicated leukoplakia in the urinary tract (bladder) (Escat and Allemann), leukoplakia of the renal pelvis nearly always has an associated infection. Some authors have given the bacteriology especial mention; the type of organism probably is of small consequence, there being such a variation in bacteriologic data in the collected case reports. It is a fact that there

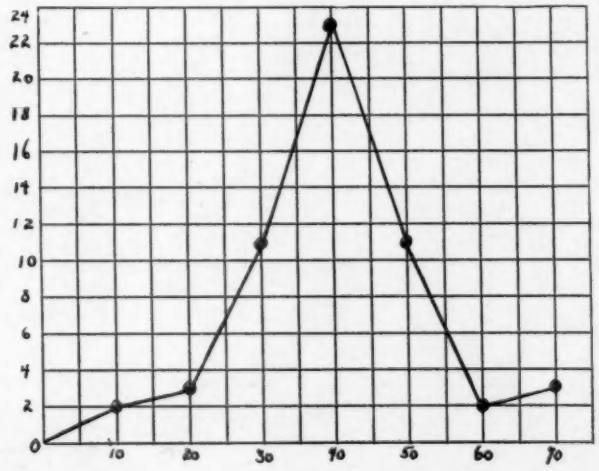

Fig. 7.—Curve, showing the age incidence in fifty-five collective cases of leukoplakia of the renal pelvis.

is an infection present which is of importance and has made most observers feel that it plays an important part in the pathogenesis. The frequent presence of cystitis, pyonephrosis, tuberculosis, lithiasis, etc., is to be noted. Table 1 shows an analysis of the sixty-seven collected cases which are distributed as follows: cystitis, forty-four; pyonephrosis, forty-one; stone, twenty-five; hydronephrosis, thirty-one; tuberculosis, ten; carcinoma, eight.

This analysis emphasizes the coexistence of infection and stone with the leukoplakia and points strongly toward the possibility of this process being an etiologic irritative factor. The finding of five squamous cell carcinomas (Kischensky, Spiess, Thomson-Walker, Aschner and Patch), one adenocarcinoma (Fuetterer) and two vesical squamous cell carcinomas (Rona and Recktenwald) are evidence supporting Hinman

TABLE 1.—*Conditions Associated with Leukoplakia of the Renal Pelvis*

Case	Author	Cystitis	Tuberculosis	Hydronephrosis	Pyelonephritis Pyonephrosis	Stone	Carcinoma	Leukoplakia Elsewhere	Miscellaneous
1	Allemann	+	..	..	+	..	..	Generalized	Uremia
2	Allemann	..	..	..	+	..	..	..	..
3	Allemann	+	..	..	+	..	..	..	..
4	Aschner	+	..	+	..	+	Squamous cell carcinoma in ureter	Bladder	Bifid pelvis
5	Beer	+	..	..	..	..	..	..	Orthostatic albuminuria
6	Beer	..	+	..	..	..	..	..	..
7	Beselin	+	+	+	..	..	..	..	..
8	Braatz	+	..	..	+	..	..	..	Interstitial nephritis
9	Biondi	..	..	+	+	..	..	..	..
10	Briggs and Maxwell	+	..	..	+	..	..	..	Addison's disease
11	Briggs and Maxwell	+	..	..	+	..	..	..	..
12	Busse	..	..	..	..	..	..	..	No data given
13	Chiari	+	..	..	+	+	..	Ureter and bladder	Both renal pelves dilated
14	Chiaudano	+	..	..	+	..	..	..	Nephritis at age of 16 years
15	Chiaudano	+	..	+	..	..	..	..	..
16	Corsdress	+	..	+	+	..	..	..	..
17	Crabtree	..	..	..	..	..	..	..	No associated pathologic condition of any type; hematuria the only sign present
18	Cummings	+	..	+	+	In bladder	..	..	..
19	Ebstein	+	+	..	..	..	..	..	Cystic cystica
20	Ebstein	..	..	+	+	..	..	Ureter	Ureteral stricture and periureteritis
21	Francke	+	..	Bilateral	..	In bladder	..	..	Uremia
22	Fulci	..	..	+	..	+	..	..	..
23	Fuetterer	..	..	..	..	+	Adenocarcinoma	..	..
24	Hallé	+	..	..	..	+	..	Both ureters and bladder	..
25	Hallé	..	..	..	..	In bladder	..	Both pelves, ureter and bladder	..
26	Halié	..	..	..	+	+	..	..	..
27	Hinman	+	..	+	+	+	..	..	..
28	Hinman, Kutzmann and Gibson	+	..	+	+	..	..	Bladder	..
29	Hinman, Kutzmenn and Gibson	+	..	+	+	..	..	..	Right nephroptosis
30	Israel	+	..	+	+	+	..	..	..
31	Israel	..	..	..	..	+	..	..	Double kidney pelvis; uremia
32	Jura	..	..	+	..	In ureter	..	..	..
33	Karo	..	..	+	..	..	..	In ureter	..
34	Keane and Denis	+	..	+	+	..	..	In ureter	Ureteritis
35	Kischensky	+	..	+	+	..	Squamous cell carcinoma of pelvis	In ureter	..
36	Kraul	+	..	+	+	..	..	..	..
37	Kretschmer	+	+	..	..	..	..	..	..
38	Kretschmer	+	..	+	..	..	..	..	..
39	Kretschmer	+	+	..	+	..	..	..	..
40	Kretschmer	+	..	+	..	+	..	..	Ureteral stricture, also attacks of urethral calculi

TABLE 1.—*Conditions Associated with Leukoplakia of the Renal Pelvis—Continued*

Case	Author	Cystitis	Tuberculosis	Hydronephrosis	Pyelonephritis Pyonephrosis	Stone	Carcinoma	Leukoplakia Elsewhere	Miscellaneous
41	Kretschmer	+	..	+	..	..	..	Ureter	Median bar at vesical neck
42	Klug	..	..	+	..	+	..	..	..
43	Klug	+	+	..	+	..	..	..	..
44	Kuettner	+	..	+	+	+	..	..	..
45	Kutzmann	+	..	..	+	..	..	..	..
46	Lavonius	+	..	..	+	+	..	..	..
47	Lavonius	.	+	..	+			.	
48	Lavonius	+	..	..	+	..	..	Ureter	
49	Lavonius	..	+	..	+	..	..	..	..
50	Lavonius	..	+	..	+	..	..	..	..
51	Leber	..	..	..	..	..	..	Eye	Congenital
52	Lecène	+	..	+	+	..	..	..	..
53	Liebenow	+	..	..	+	+	..	Generalized	Uremia; urethral fistula
54	Michon	..	..	..	..	..	..	..	No data given
55	Patch	+	..	..	+	Kidney, ureter and bladder	Squamous cell carcinoma of left kidney and bladder	Both kidneys and bladder	Uremia; obstruction at vesical neck
56	Pedroso and Lequerica	..	..	..	+	+	..	..	..
57	Pedroso and Lequerica	..	..	+	+	..	..	..	..
58	Pollack	..	..	..	..	..	..	..	No data given
59	Rafin	+	..	+	..	+	..	..	..
60	Recktenwald	+	..	+	..	..	Squamous cell carcinoma of bladder	..	..
61	Richey	+	..	+	+	..	..	..	..
62	Romiti	+	..	+	+	+	..	..	Foreign body in renal pelvis
63	Rona	+	..	+	+	Kidney and ureter	..	Left ureter	..
64	Rona	+	+	..	+	..	Squamous cell carcinoma of bladder	..	Pulmonary and genitourinary tuberculosis
65	Spiess	..	..	..	+	+	Squamous cell carcinoma of pelvis	..	..
66	Stockmann	+	..	..	+	..	..	..	Right ureter dilated
67	Thomson-Walker	+	..	+	+	+	Squamous cell carcinoma of pelvis	..	..
Total.....		44	10	31	41	25	8	16	

and Gibson's idea that leukoplakia is not altogether a physiologic but also a pathologic process. Miscellaneous associated conditions have been orthostatic albuminuria (Beer), interstitial nephritis (Braatz), cystitis cystica (Ebstein), double renal pelvis (Israel), infancy (Leber), foreign body in the renal pelvis (Romiti), calculus in the opposite kidney and ureter (Rona) and Addison's disease (Briggs and Maxwell).

Symptomatology.—There are no pathognomonic symptoms of leukoplakia of the renal pelvis. Most cases present the signs and symptoms of the coexisting or associated condition, the usual one being a urinary infection of long duration. The true condition is almost never diagnosed except at operation or autopsy. An exception

TABLE 2.—*Leukoplakia of the Renal Pelvis*

Case	Author	Date	Age, Years	Sex	Side	Initial Symptoms	Duration	Anatomy
1	Allemann	1926	28	M	Left	Dull pain in region of kidney; hematuria	.....	Leukoplasia of renal pelvis with suppurative nephritis
2	Allemann	1926	27	M	Right	Hematuria and cystitis	10 years	Typical leukoplasia of pelvis with areas of pus in parenchyma
3	Allemann	1926	..	F	Bilateral	Acute and persistent cystitis	.....	Complete epidermization from urethra up to both renal pelves; bilateral hydro-ureter and pyelonephritis with cortical abscesses
4	Aschner	1922	38	M	Right	Attacks of stabbing pain in right flank	3 weeks	Lower pelvis and calices contain grayish-white, greasy flakes; mucosa almost covered by dull, grayish-white, elevated irregular membrane; squamous cell carcinoma at ureteropelvic junction, infected hydronephrosis, calculi
5	Beer	1914	20	M	Left	Orthostatic albuminuria; cystitis	3 years	Pearly white plaques in the urine
6	Beer	1914	35	M	Left	Pain in left flank, radiating to scrotum	9 months	Leukoplakia with lower half of the pelvis, about the size of a silver dollar, associated with tuberculosis
7	Beselin	1885	35	M	Right	Attacks of renal colic	17 years	Hydronephrosis; pelvis covered with white pearly membrane; also tuberculosis
8	Biondi	1904	..	..	.....	.....	.....	Greater part of pelvis lined with a leukoplakia; pyelonephritis; hydronephrosis
9	Braatz	1898	33	F	Right	Attacks of renal colic	2 years (?)	Pelvic mucous membrane had appearance of epidermis; interstitial nephritis
10	Briggs and Maxwell	1926	37	F	Left	Attacks of renal colic; cystitis	12 years	Pelvis lined with stratified squamous epithelium; pyelonephritis with pyelectasia; Addison's disease
11	Briggs and Maxwell	1926	37	F	Right	Renal pain on right side	13 years	Renal pelvis lined with typical stratified squamous epithelium, showing considerable cornification; pyonephrosis
12	Busse	1904	..	..	.....	.....	.....	Parts of renal pelvis showed a leukoplakia; renal calculi
13	Chiari	1888	34	F	.....	Pyelitis and cystitis...	.....	Hydronephrosis; mucous membrane thick and epidermoid; also renal calculus
14	Chiaudano	1924	37	M	Right	Nephritis at 16 years of age; occasional burning on urination	21 years	The lower two thirds of the pelvis and part of ureter showed a rough whitish, shiny and macerated, epidermis-like membrane; pyonephrosis with abscesses in renal parenchyma
15	Chiaudano	1924	..	..	Right	Intermittent pyuria and pain in right kidney	11 years	Well defined areas of leukoplakia scattered over whole pelvis; infected hydronephrosis
16	Corsdress	1923	45	F	Left	Renal colic	3 years	Hydronephrosis; island of flattened epithelium at the ureteropelvic junction, forming almost a plug in ureter
17	Crabtree	1929	40	M	.....	Hematuria	.....	Leukoplakia extending from pelvis 2½ inches down the ureter; no associated pathologic condition found
18	Cummings	1923	28	M	Left	Frequency and burning on urination	3 years	Vesical calculus and cystitis; leukoplakia of entire mucous membrane of pelvis
19	Ebstein	1882	20	F	.....	.....	.....	Definite small raised areas of shiny mucous membrane; hydronephrosis and hydro-ureter
20	Ebstein	1882	48	..	Right	.....	.....	White shiny raised area of cornified epithelium in right pelvis; also pyelitis, ureteritis and pyelitis cystica
21	Francke	1926	44	M	Right	.....	Several years	Entire renal pelvis and ureter covered with leukoplakia; hydronephrosis; vesical calculus and contracted bladder
22	Fulci	1909	..	..	.....	.....	.....	Hydronephrotic sac lined with flat epithelium and found to contain round pearl-like elements; old hydronephrosis and stones
23	Fuetterer	1905	..	..	... ..	.....	.....	Plaques of leukoplakia in renal pelvis; stone and adenocarcinoma

24	Hallé.....	1896	39	M	Bilateral	Incontinence at 4 years of age; cystitis at 22 years; passage of sand	5 years	Leukoplakia of right pelvis and both ureters; bilateral hydronephrosis
25	Hallé.....	1896	70	M	.....	Urinary incontinence for 25 years; vesical calculus removed 18 months ago	25 years (?)	Leukoplakia of both pelves and ureter
26	Hallé.....	1896	..	..	.....	.....	.....	Pelvic mucous membrane was thick, white and irregular; calculous pyelonephritis
27	Hinman.....	1923	37	F	Right	Passage of gravel during pregnancy	10 years	One small area in renal pelvis showing the normal transitional epithelium gradually changing to the squamous type; calculous hydronephrosis and chronic pyelonephritis
28	Hinman, Kutzmann and Gibson	1923	38	M	Right	Nocturia (once or twice)	20 years	Entire pelvic wall is covered with a thick wrinkled epidermoid sheet; hydronephrosis and hydro-ureter
29	Hinman, Kutzmann and Gibson	1923	34	F	Right	Suprapubic distress ...	9 years	Renal pelvis was filled with white scaly débris from leukoplakic membrane covering pelvic wall
30	Israel.....	1901	50	F	Right	Puerperal cystitis	.....	Dry shiny pearly wrinkled surface at ureteropelvic junction; pyonephrosis
31	Israel.....	1901	49	F	.....	.....	.....	Epidermization of lower pelvis in a double kidney; nephrolithiasis
32	Jura.....	1924	32	F	Left	Hematuria; pain in the left flank	Many years	Whitish leukoplakic patch at ureteropelvic junction; hydronephrosis; stone in lower left ureter
33	Karo.....	1926	35	M	Right	Piercing pains in region of the right kidney; frequency	8 years	Nearly entire pelvic mucous membrane showed wide, confluent areas of thick, epidermizing membranous covering; hydronephrosis
34	Keane and Denis.....	1928	37	F	Right	Pain in right lower quadrant; nausea and some frequency	7 years	Large kidney, showing an infected hydronephrosis; pelvic mucosa had a covering of leukoplakia extending down the ureter: chronic diffuse pyelonephritis
35	Kischensky.....	1901	32	F	Right	Pain in region of right kidney	1½ months	Cornification of calices; pelvis filled with squamous cell carcinoma; infected hydronephrosis
36	Kraul.....	1922	28	..	Right	Occasional pain in right kidney	Several years	Mucous membrane of posterior pelvic wall showed area of leukoplakia; infected hydronephrosis
37	Kretschmer.....	1922	40	F	Right	Bladder distress	3 years	Large patch of leukoplakia about ureteropelvic junction extending to calices and ureter; tuberculosis
38	Kretschmer.....	1922	26	M	Right	Hematuria following influenza	4 years	Area of leukoplakia on posterior pelvic wall; hydronephrosis; cystitis
39	Kretschmer.....	1928	34	F	Left	Terminal burning on urination, frequency and urgency	1 year	In renal pelvis at level of middle calyx was an area of leukoplakia 2 inches (5 cm.) in diameter; tuberculosis; pyonephrosis
40	Kretschmer.....	1928	41	M	Left	Frequency, burning and tenesmus	5 years	Superior calices and lower part of pelvis had a dull china-white covering; infected hydronephrosis and stone; ureteral stricture
41	Kretschmer.....	1928	61	M	Right	Renal colic and passage of gravel	35 years	Renal pelvis and ureter showed longitudinal wrinkles and folds of leukoplakia; infected hydronephrosis
42	Klug.....	1922	40	F	Right	Pain in right renal area	4 months	Most of pelvic mucosa covered by a skinlike formation; some of calices filled with atheromatous material; hydronephrosis; nephrolithiasis
43	Klug.....	1922	39	M	Right	Inflammation of cecum and appendix	2 years	Whole pelvis thickened, leather-like and swollen; pelvis contained fatty, shiny cholesteatomatous material; tuberculosis
44	Kuettner.....	1929	35	M	.....	Cystitis due to gunshot wound	1¼ years	Pelvis covered with granulations; infection had destroyed the leukoplakic covering; soft calculi and pyonephrosis
45	Kutzmann.....	1929	26	F	Left	Pain in left kidney region and frequency	3 years	Pelvis and cavity-like calices are covered with a whitish wrinkled thick parchment-like membrane; pyonephrosis
46	Lavonius.....	1913	40	F	Right	.....	6 months	Entire renal pelvis covered with leukoplakia; calculus; pyonephrosis

TABLE 2.—*Leukoplakia of the Renal Pelvis—Continued*

Case	Author	Date	Age, Years	Sex	Side	Initial Symptoms	Duration	Anatomy
47	Lavonius.....	1913	16	F	Right	.....	1 year	A small part of the lower portion of renal pelvis shows a leukoplakia; renal tuberculosis
48	Lavonius.....	1913	47	F	Left	.....	18 years	Entire renal pelvis and ureter involved with leukoplakia; chronic pyonephrosis
49	Lavonius.....	1913	29	M	Right	.....	9 months	Patches of leukoplakia in the lower two calices; right renal tuberculosis
50	Lavonius.....	1913	22	F	Right	.....	2 years	A small strip of leukoplakia, 2 cm. long, in upper part of renal pelvis; right renal tuberculosis
51	Leber.....	1883	4 mo.	F	.....	.....	.....	Renal papillae and calices covered with thick white epidermis; associated with leukoplakia of the eye; congenital
52	Lecène.....	1913	28	F	Right	Slight pain in iliac fossa; frequency	.....	Greater part of pelvis changed to thick skin; marked infection; infected hydronephrosis
53	Liebenow.....	1891	7	M	Bilateral	Cystitis	3 years	Generalized leukoplakia of entire genito-urinary tract; urethral fistula, calculous pyelonephritis; cholesteatoma of under side of diaphragm
54	Michon.....	1914	..	..	.....	.....	.....	Multiple plaques in pelvis and down ureter
55	Patch.....	1929	47	M	Bilateral	Dysuria	16 years	Leukoplakia in both kidneys with squamous cell carcinoma in left kidney; leukoplakia and squamous cell carcinoma in bladder; severe urinary infection, calculus in right kidney and multiple calculi in bladder
56	Pedroso and Lequerica	1927	41	M	Left	Renal colic, hematuria and pyuria	3 years	Renal pelvis and calices entirely covered by a rough, pearly white membrane; pyelonephritis
57	Pedroso and Lequerica	1927	30	F	Right	Pain in right kidney region and later tenesmus	3 years	Renal pelvis and calices were covered by a thick layer of a pearly white substance wrinkled in all directions; hydronephrosis
58	Pollack.....	1901	..	..	.....	.....	.....	Formation of small islands of leukoplakia in renal pelvis
59	Rafin.....	1907	50	F	Left	.....	5 years	Entire renal pelvis showed leukoplakia; stone and hydronephrosis
60	Recktenwald.....	1909	60	M	Left	Bladder trouble	7 months	Pelvis covered with silvery membrane; hydronephrosis and hydro-ureter
61	Richey.....	1920	43	M	Right	Paroxysms of backache	22 years	Entire pelvis covered with leukoplakia; hydronephrosis and infection
62	Romiti.....	1922	25	M	Left	Persistent urinary fistula following pyelotomy	6 years	Mucous membrane of pelvis grayish white and shiny-like pearl; associated with foreign body and stone formation
63	Rona.....	1901	35	M	Left	.....	.....	Two thirds of left pelvis covered with thick pavement epithelium; stone in right kidney; hydronephrosis
64	Rona.....	1901	46	M	Right	.....	.....	Xerosis of right pelvis; squamous cell carcinoma of bladder; pyelonephritis
65	Spiess.....	1915	54	F	Left	.....	7 years	Calices showed leukoplakia; lower part of kidney showed an oxalate stone surrounded by a squamous cell carcinoma
66	Stockmann.....	1902	..	F	Right	Acute cystitis	2 years	Plaques in urine diagnosed leukoplakia; cured with lavages of silver nitrate
67	Thomson-Walker....	1927	63	M	Right	Calcuric and lumbar pain	27 years	Pelvic lining showed leukoplakia which passed into squamous carcinoma with cell nests; calculous pyonephrosis

to this is Stockmann's and Beer's cases in which cornified epithelial plaques were found in the urine, causing some observers to consider the passage of these as pathognomonic of leukoplakia.

Nearly all patients complain of dysuria, burning on urination, frequency, urgency and similar urinary disturbances, all of which are due to the associated infection (pyelitis, pyelonephritis, pyonephrosis, cystitis and lithiasis), the presence of which may have persisted over many years. Lumbar pains and backache varying from the dull type to the acute renal colic are encountered. The latter has been thought to be due in some cases to small leukoplakic plaques moving down the ureter. The urine nearly always shows infection and pyuria. Hematuria occurred in twenty-four of the sixty-seven reported cases (35.8 per cent). It was found in eleven of forty cases of pyonephrosis and pyelonephritis, five of thirty-one of hydronephrosis, nine of twenty-four of stone, four of ten of tuberculosis and one of seven of malignant disease. While in this analysis hematuria is shown to be due probably to the existing associated condition, it should nevertheless be considered as a significant sign.

Careful urologic examination and study are imperative to determine the exact status of the urinary tract and for the diagnosis of the associated condition. The leukoplakic process, if confined only to the renal pelvis, will remain undiagnosed in most cases. Careful cystoscopic examination of the bladder may occasionally give a clue. Leukoplakia may be noted here, the observer finding the irregular plaque membranous formation, varying in luster from a dirty white to gray, raised from either a normal or an infected vesical mucous membrane. The silvery gray luster of these areas causes them to stand out from the adjacent tissues. Close observation will show no blood vessels coursing through these areas. The possibility of finding a leukoplakia should always be borne in mind in all long-standing and chronic cases of urinary infection, and a careful pathologic examination should be made of all material removed from the kidney at operation. This method of procedure would probably prove that leukoplakia of the renal pelvis was of more frequent occurrence.

Treatment.—Since it is not possible to diagnose leukoplakia of the renal pelvis as such, treatment must be directed toward the associated condition. The infectious process has usually destroyed the kidney beyond repair; if the condition is unilateral, nephrectomy is the procedure indicated. The relationship of leukoplakia to malignant disease (squamous cell carcinoma) should also be borne in mind when treatment is instituted. It has been found useless to treat these patients conservatively, because the associated condition has usually been present for a long period.

If there are any contraindications to surgical treatment, such palliative measures as pelvic lavage with a weak solution of silver nitrate or removal of the desquamating membrane by curettement may be instituted. Fulguration and application of radium has given only limited success in vesical cases. Stockmann reported a cure after twenty-one lavages of the renal pelvis with 5 per cent solution of silver nitrate.

SUMMARY

1. Leukoplakia of the renal pelvis is of importance because of its unknown etiology and pathogenesis, its difficulties in diagnosis and treatment and its relationship to malignant disease.

2. Leukoplakia signifies the formation of white patches on the mucous membranes, that is, an epidermization of the mucosa with keratinization and desquamation.

3. Leukoplakia of the renal pelvis is only relatively rare, sixty-seven cases being collected to date. This probably represents only a part of a number of cases unrecognized or not reported.

4. Leukoplakia of the renal pelvis is associated with a chronic urinary infection or lithiasis; hence the clinical picture is one of urinary infection and chronicity.

5. Leukoplakia of the renal pelvis occurs most frequently in the fourth decade of life, is found equally in both sexes and occurs equally in both kidneys.

6. There are two principal theories concerning the etiology of leukoplakia: (*a*) The process is one of metaplasia or adaptation and protection by cornification to a chronic irritative inflammatory environment. (*b*) Leukoplakia is of congenital origin, being due to misplaced embryonal cell rests from the primitive ectoderm.

7. The treatment is that employed for the associated condition, nephrectomy usually being carried out if the condition is unilateral. Palliative measures such as pelvic lavage have been used. Fulguration and radium have given limited success in vesical cases.

8. One new case of leukoplakia of the renal pelvis is reported.

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OXYGEN CONTENT OF BLOOD IN PATIENTS WITH VARICOSE VEINS *

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The pathogenesis of varicose veins and the concomitant abnormalities of the circulation are not clearly understood. My purpose in this paper is to record observations made in the course of study of the blood gases in a series of patients with apparent abnormalities of the veins of the extremities. Although these observations are insufficient for significant conclusions concerning the pathogenesis of conditions peculiar to varicose veins, they are sufficient for definite conclusions concerning certain fundamental facts that must be considered hereafter in similar studies.

Most of the observations on the gases of the blood of peripheral vessels have been made for normal persons, and usually the blood of the upper extremities has been studied. De Takáts, Quint, Tillotson and Crittenden [1] recently reported studies in which the carbon dioxide and oxygen contents of the blood of varices of the leg were compared with those of the blood from the cubital vein of the arm. They stated: "The carbon dioxide content of the varicose blood is definitely higher than that of the venous blood in the cubital vein of the same person. The reverse is true of the oxygen content." In normal subjects they found the same carbon dioxide content in samples of blood from the cubital and saphenous veins. The oxygen content of the blood from these veins was apparently assumed to be the same. Goldschmidt and Light [2] found marked differences in the carbon dioxide and oxygen content of samples of blood from closely adjacent veins of the forearm. They stated: "Closely adjacent veins of the forearm may exhibit differences in their content of blood gases. The carbon dioxide and oxygen contents of two bloods, drawn consecutively from the hand and bend of the elbow, may vary independently." They found that the dependent position of the arm, even with the development of venous engorgement had little effect on the average gaseous content of the

* Submitted for publication, May 21, 1929.

* From the Department of Surgery, Vanderbilt University.

1. De Takáts, Geza; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

2. Goldschmidt, S., and Light, A. B.: A Comparison of the Gaseous Content of Blood from Veins of the Forearm and the Dorsal Surface of the Hand as Indicative of Blood Flow and Metabolic Differences in These Parts, Am. J. Physiol. **73**:127, 1925.

blood from the veins of the forearm. De Takáts and his co-workers did not state the position of their subjects when the samples of blood were drawn.

METHOD OF STUDY

The observations recorded in this paper were obtained from the study of several normal persons and ten subjects with varicose veins. In the patients with varicose veins the disease was limited to one extremity, except in two instances in which it was much more marked on one side. Patients with symmetrical disease were considered as unsuitable for this study. The extent of the clinical manifestations as regards the varicosities and ulceration is indicated in the individual protocols.

The same method of procedure was carried out when possible in each person studied. Samples of blood were drawn from the femoral, saphenous and superficial veins of the leg in both the recumbent and standing postures. If the patient was standing, an attempt was made to obtain the samples of blood as nearly simultaneously as possible; if this was impossible, it was attempted to have the patient stand for the same period of time when samples from the corresponding veins were withdrawn. Samples of venous blood were collected without stasis. Precautions against contact with air were observed. The blood gas analyses were performed with the Van Slyke-Neill manometric apparatus.

The study of the normal persons was only for the purpose of obtaining observations before the study of abnormal cases. The results obtained are not to be considered in the sense of establishment of a normal standard of blood gas content, but only for the purpose of determining the effect of position. In these persons, blood from the femoral veins only was analyzed. Only the observations on one normal subject are recorded in this paper; others studied gave similar results.

In the ten patients with varicose veins, samples of blood were withdrawn from the femoral veins; in two of these, no attempt was made to obtain blood from other localities. Samples were obtained from at least one other vein in the remaining instances. When the figure for the oxygen content of the blood from the saphenous vein or from one of the superficial veins of the lower part of the leg on the diseased side is given without the figure for a corresponding vein of the normal side, it is because the vein of the normal side could not be seen without the production of constriction which would vitiate the result. Six of the ten patients with varicose veins had ulcerations of the lower part of the leg, and one had had previous ulceration.

OBSERVATIONS

Since the effects of changes in posture were studied on the patients with varicose veins, similar studies were made on people without such disease. An example of such a study is given in table 1.

This table shows that the oxygen content falls rapidly when the patient stands, and rises when the patient again assumes the recumbent position.

CASE 1.—J. W., a colored man, aged 65, entered the hospital because of several small ulcers and many prominent veins on the lower part of the left leg. The left saphenous vein felt cordlike. Several veins of the lower part of the right leg were a little more prominent than normal. The left leg was slightly larger than the right. The patient had active pulmonary tuberculosis. The Wassermann reaction was positive.

Samples of blood were obtained from the femoral and saphenous veins and from superficial veins of the lower part of both legs. The results are given in table 2.

It is to be noted that the oxygen content of the venous blood from the femoral vein of the left or diseased side is higher than that on the opposite side. The oxygen content of the blood from the superficial veins of the lower part of the legs was slightly lower on the ulcerated side.

TABLE 1.—*The Effects on Content of Blood Gases of Changes in Posture in a Patient Without Varicose Veins; Sample of Blood from Right Femoral Vein*

Position	Carbon Dioxide Content, Volumes per Hundred Cc.	Oxygen Content, Volumes per Hundred Cc.	Saturation, Per Cent
Recumbent	49.96	15.80	..
	.....	14.33	85
	.....	15.69	..
Upright for one minute	50.53	10.74	58
Upright for two minutes	.....	7.23	39
Upright for two and one-half minutes	51.76	6.88	37
Recumbent for one minute	49.43	11.76	63

TABLE 2.—*Oxygen Content in Patient (J. W.) with Varicose Veins and Ulcers of the Left Leg*

Vein	Recumbent		Standing	
	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent
			Standing 5 minutes	
Right femoral	8.40	52.7	5.28	33.2
			Standing 6 minutes	
Left femoral (diseased side)	8.64	54.2	7.70	48.3
			Standing 4 minutes	
Right saphenous	.....	....	3.87	24.3
			Standing 5½ minutes	
Left saphenous (diseased side)	11.34	71.2	8.87	55.6
			Standing 6 minutes	
Lower part of the right leg	8.36	54.5	6.66	41.8
			Standing 3 minutes	
Lower part of the left leg (above ulcer)	.....	....	6.06	38.0
			Standing 4 minutes	
Lower part of the left leg (above ulcer)	.....	....	5.46	34.3

CASE 2.—B., a white man, aged 24, entered the hospital because of varicose veins and ulcers of the lower part of the left leg of about five years' duration. The ulcers were very superficial and the foot had a cyanotic appearance. The saphenous vein was easily visible. There was no immediate filling of the saphenous vein when the leg was suddenly lowered, with the saphenous opening occluded. The Wassermann reaction was positive.

Samples of blood were drawn from the femoral, saphenous and superficial veins of the lower part of the legs and of the ankles. The results are given in table 3.

It is to be seen that whereas the oxygen content of the blood from the femoral veins is slightly lower on the diseased side, it is higher in

the saphenous vein of this leg. As was true of the previous case, the oxygen content is lower in the region of the ulcer than at a similar level on the opposite side.

CASE 3.—P., a white woman, aged 44, complained of varicose veins and a small ulcer of the lower part of the left leg. She first noticed the dilated veins fifteen years before entry, and the ulcer had been present for six months. The small ulcerated area was located just below a large bunch of varicose veins on the anterior surface of the middle third of the lower part of the left leg. The left saphenous vein was easily visible when the patient stood. The left saphenous

TABLE 3.—*Oxygen Content in Patient (B.) with Varicose Veins and Ulcers of the Left Leg*

Vein	Recumbent		Standing	
	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent
Right femoral	14.66	77.0	6.04	31.7
Left femoral (diseased side)	13.21	69.4	5.92	31.1
Right saphenous	.....	....	8.53	44.8
Left saphenous (diseased side)	13.87	72.9	11.28	59.3
Middle of the right leg	.....	....	11.16	58.6
Middle of the right leg (above ulcer)	.....	....	7.26	38.1
Right ankle	.....	....	11.10	58.3
Left ankle (below ulcer)	.....	....	6.88	36.1

TABLE 4.—*Oxygen Content in Patient (P.) with Varicose Veins and Ulcers*

Vein	Recumbent		Standing	
	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent
Right femoral	13.88	73	10.90	60
Left femoral (diseased side)	16.05	89	14.74	81
Left saphenous (diseased side)	.....	..	9.84	54
Lower part of the right leg	.....	..	10.41	57
Lower part of the left leg (diseased side)	15.12	83	11.16	62

Twenty-six days after removing dilated veins and ulcer of the lower part of the left leg

Vein	Recumbent		Standing	
	Oxygen Content	Saturation	Oxygen Content	Saturation
Right femoral	.....	..	11.34	63
Left femoral (diseased side)	.....	..	12.16	67

vein did not fill rapidly when the leg was suddenly lowered after being elevated, but the dilated veins of the lower part of the leg filled immediately. The left leg was larger than the right.

Samples of blood were drawn from the femoral and saphenous veins and veins of the lower part of the legs. The results are listed in table 4.

The oxygen content of the blood from the femoral veins was higher on the diseased side, and this difference was less marked after the dilated veins and the small ulcer had been removed from the lower part of the left leg. There was little difference in the oxygen content of samples obtained before operation from veins of the lower part of both legs.

CASE 4.—V. W. B., a colored man, aged about 35, entered the hospital because of varicose veins and ulcers of the right leg. The varicosities were first noticed sixteen years previously. The entire right leg and thigh were larger than the left. The ulcerated areas covered the greater part of the circumference of the leg. The Trendelenberg test indicated incompetence of the deeper veins. Several observers obtained different figures for the blood pressure in the two legs, but all agreed that it was higher on the diseased side. The Wassermann reaction was positive.

Samples of blood were drawn from veins at various levels on both legs. The results are given in table 5.

This table shows that the oxygen content is consistently higher in the extremity with varicose veins and ulcerations. Changes in posture caused little alteration in the oxygen content of the venous blood on the diseased side, and the figures were nearly the same whether the

TABLE 5.—*Oxygen Content in Patient (V. W. B.) with Varicose Veins and Ulcers*

Vein	Recumbent: Oxygen Content, Volumes, per Hundred Cubic Centimeters	Standing: Oxygen Content, Volumes, per Hundred Cubic Centimeters
Right femoral (diseased side)	14.02	13.79
Left femoral	13.25	6.86
	.....	7.15
Right saphenous, upper part of the thigh (diseased side)	15.00	12.05
	.....	13.76
	.....	13.79
Right saphenous, middle of the thigh (diseased side)	.....	14.33
Right saphenous, at knee (diseased side)	.....	15.32
Lower part of right leg (diseased side)	.....	15.27
Lower part of the left leg	.....	8.95
Right ankle (diseased side)	.....	15.04
Left ankle	.....	10.04

samples were taken from the upper or lower part of the leg. Due to the fact that the patient had a positive Wassermann reaction and also because the ulcers were not entirely characteristically varicose, there was some doubt as to the diagnosis. It can be stated with certainty, however, that there were many prominent dilated veins.

CASE 5.—H. H., a white man, aged 30, entered the hospital because of claw feet. It was noted on examination that he had several prominent veins on the anterior surface of the lower part of his left leg. Both feet had a cyanotic appearance. He had no ulceration at the site of the varicose veins. The two legs were apparently the same size.

With the patient standing, samples of blood were drawn from the right and left femoral veins and from veins at the level of the middle third of the lower part of both legs. The figures are given in table 6.

The blood from the femoral vein on the side with varicose veins had a higher oxygen content than that from the opposite side, but the reverse was true for the blood from the lower part of the legs.

CASE 6.—J. W. T., a white man, aged about 50, entered the hospital because of an inguinal hernia. Some of the veins of the lower part of the right leg and the saphenous vein were prominent. There was no ulceration. Samples of blood were drawn from the two femoral veins with the patient standing. The oxygen content of the blood collected from the right femoral vein, on the diseased side, was 9.77 volumes per hundred cubic centimeters, while that from the left was 6.96 volumes. There was no marked difference in the size of the two legs.

CASE 7.—T. C., a colored woman, entered the hospital because of a small ulcer on the lower part of her left leg which appeared six weeks before, following a local injury. She had had several prominent veins in this area for nine years. There were no enlarged visible veins in the right leg. The left leg was slightly larger than the right.

While the patient stood, samples of blood were drawn from the femoral veins and from veins of the lower part of the legs. The figures are given in table 7.

TABLE 6.—*Oxygen Content of the Blood in Patient (H. H.) with Varicose Veins Without Ulceration*

Vein	Standing	
	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, per Cent
Right femoral	4.95	25
Left femoral (diseased side)	5.55	28
Lower part of the right leg	13.41	68
Lower part of the left leg (diseased side)	10.24	53

TABLE 7.—*Oxygen Content of the Blood in Patient (T. C.) with Varicose Veins and Ulcer*

Vein	Oxygen Content, Volumes, per Hundred Cubic Centimeters
Right femoral	10.43
Left femoral (diseased side)	13.97
Lower part of the right leg	5.49
Lower part of the left leg (diseased side)	5.49

The oxygen content of the femoral venous blood was higher on the side with varicose veins. The content of the blood from the lower part of the leg was the same on both sides.

CASE 8.—A colored woman, aged 20, had a localized patch of dilated veins at the posterior surface of the left knee. There were no markedly dilated veins of the lower part of the legs and no ulceration. Samples of blood were drawn from the two femoral veins with the patient lying down. The oxygen content of the blood from the right femoral vein was 10.26 volumes per hundred cubic centimeters and that of the left (diseased side), 10.68 volumes. The oxygen content of the blood from one of the dilated veins with the patient standing was 11.52 volumes.

CASE 9.—W. L., a white man, aged 59, entered the hospital because of varicose veins of the right leg of fifteen years' duration. He also had a small ulcer just above the right ankle. The right leg was definitely larger than the left. There had been previously a large ulcerated area on this leg, and the area was markedly

discolored and hard at the time of examination. The saphenous vein was enlarged and hardened. A large mass of veins was easily seen just above the discolored area. With the patient lying down, the oxygen content of the right femoral vein (diseased side) was 11.1 volumes per hundred cubic centimeters, and that of the left (apparently entirely normal side) 10.2 volumes. The oxygen content of the blood from one of the dilated veins above the ulcer was 16.14 volumes per hundred cubic centimeters, and from a dilated vein on the right foot distal to ulceration it was 16.32 volumes. Blood could not be obtained from the small veins of the left foot and leg. Corrected venous pressures obtained with a citrate monometer showed the following readings for a dilated vein of right leg: with the patient standing, 32 cm. of water; with the patient recumbent, 17 cm. of water.

CASE 10.—J. E. L., aged 65, entered the hospital because of ulcers and swelling of the lower part of the right leg. He first noticed large tortuous veins on the

TABLE 8.—*Oxygen Content of the Blood in Patient (J. E. L.) with Thrombosis of the Inferior Vena Cava*

Vein	Recumbent		Standing	
	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent	Oxygen Content, Volumes, per Hundred Cubic Centimeters	Saturation, Per Cent
			Standing 12 minutes	
Right femoral	11.80	78.0	5.72	37.8
			Standing 5 minutes	
Left femoral	6.43	42.5	3.33	22.0
			Standing 4 minutes	
Lower part of the right leg	12.34	82.0	9.89	65.5
			Standing 2 minutes	
Lower part of the left leg	8.34	55.0	8.82	57.0
Repeat observation			Standing 4 minutes	
Lower part of the left leg	.....	....	6.85	45.0
Repeat observation			Standing 3 minutes	
Lower part of the left leg	.....	....	6.67	44.0
Repeat observation			Standing 10 minutes	
Vein above umbilicus	12.04	80.0	4.05	27.0
Left circumflex	11.09	74.0	....	....
			Standing 7 minutes	
Right femoral artery	.....	....	13.95	92.0
Left femoral artery	14.55	....	.....	....

lower part of the right leg, thirty-five years previously. During the past fifteen years, he had many ulcers of this leg, which disappeared and reappeared frequently. The right leg became quite swollen about six days prior to his admission to the hospital. Eighteen years before, prominent veins on the abdomen and lower part of the chest were noticed, and ten years before, the veins of the lower part of the left leg were thought to be enlarged. Several ulcers which healed rapidly appeared during this time on the left leg.

On examination, many prominent veins were seen over the lower part of the chest and abdomen. The direction of the blood stream in these veins was upward. Phenolsulphonphthalein injected into a vein of the lower leg could be recovered almost immediately from one of the dilated veins in the region of the umbilicus. There were many prominent veins of the lower part of both legs. On the left leg the scars of healed ulcers were seen, but there were no open areas. There were several open ulcers of the lower part of the right leg and a large area of hyperkeratosis in the region of the internal malleolus. The right saphenous vein felt cordlike. A diagnosis of thrombosis of the inferior vena cava was made.

The results of the analyses on various samples of blood are given in table 8.

This table shows that the venous blood from the extremity with the larger varicose veins and the ulcerations had a higher oxygen content than the opposite side.

To summarize briefly, in nine of the ten cases observed, the oxygen content of the blood from the femoral veins was higher on the diseased side or more diseased side than on the opposite side. This relationship held in both the standing and the recumbent postures. Changing from the recumbent to the standing position resulted in a smaller drop in the oxygen content of the diseased side than in that of the normal side. In the instances in which it was determined, the oxygen content of the blood from the saphenous vein was higher on the diseased side. No definite relationship seems to hold between the oxygen content of the blood of the dilated veins of the lower part of the leg and similarly located normal veins of the opposite leg, but the impression is gained that the oxygen content is lower on the diseased side when there is no ulceration and usually higher when there is ulceration. More cases will have to be studied in order to determine this point.

SUMMARY

1. The oxygen content of the venous blood of the femoral vein is highest when the patient is in the recumbent posture and decreases rapidly when the upright position is assumed.

2. In patients with unilateral varicose veins of the lower extremities, the venous oxygen content is higher in the femoral vein of the diseased side. This difference is usually accentuated when ulceration is present. Changes in posture cause less alteration in the venous oxygen content of the diseased side. Practically the same statements may be made regarding the oxygen content of the blood of the saphenous vein.

3. When ulceration is not present, it may be stated, in general, that the venous oxygen content of varicose veins of the lower part of one extremity is lower than that of similarly placed normal veins of the opposite extremity. However, when ulceration and infection are superimposed on the varicose veins, the oxygen content is usually higher on the diseased side.

4. Studies on one case of thrombosis of the inferior vena cava with prominent veins of the lower extremities revealed data similar to those obtained in the other cases with varicose veins.

5. The observations suggest that the total flow of blood through a leg with varicose veins is increased.

CARCINOMA OF THE COLON

INTRAPERITONEAL VACCINATION BY MIXED VACCINE OF COLON BACILLI AND STREPTOCOCCI *

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Peritonitis is an urgent potentiality in any surgical maneuver for a malignant condition of the large bowel. The reasons for this group themselves mainly under three headings: (*1*) the peculiar conformation of the large bowel, which differs widely from the small intestine, both anatomically and physiologically; (*2*) the marked permeability of the large bowel when attacked by malignant disease, due either to its peculiar structure or to mucosal injury produced by large ulcerating carcinomas, and (*3*) the debilitation, dehydration and generally lowered resistance of patients who harbor neoplasms.

A glance at mortality statistics shows the necessity and desirability of adopting any measure which will, even in a small degree, tend to obviate peritoneal contamination, and it was with this in view that the isolation and individualization of cases of diseases of the colon at the Mayo Clinic were undertaken two years ago. This formation of a colonic unit has permitted us to adopt uniform measures in all cases as well as to study in detail the different types, the situation, the grades of malignancy and the technical procedures applicable to each. It has urged the adoption of numerous measures as well as the abandonment of many steps hitherto deemed satisfactory in our service. Among the details which have contributed in some measure to the reduction of mortality, and which have assured a more satisfactory outcome, has been the introduction as a routine in these cases of intraperitoneal vaccine of colon bacilli and streptococci. We believe this measure has given sufficient satisfaction to merit our reporting its employment in a series of sixty cases in which the patients were treated between June 1 and Nov. 6, 1928.

Although this is too small a series to allow us to assert dogmatically that vaccination is likely to prove of extensive benefit in malignant conditions of the colon treated surgically, we believe that as an adjuvant

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* Submitted for publication, April 15, 1929.

* Read at the Southern Surgical Association, White Sulphur Springs, Va., Dec. 11 to 13, 1928.

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to surgical procedures and as a step in the preliminary preparation of patients for radical extirpation of malignant growths, peritoneal vaccination has marked value. Because, attending its use, there has been lessening of the postoperative reaction, a smoother convalescence and lowering of actual operative mortality, it commends itself to open minded criticism and trial before condemnation.

Herrmann [1] deserves great credit for pointing out the importance of the route by which protective vaccination may be carried out against gross fecal soiling and for working out methods of vaccination which are clinically adaptable. The reported work hardly does his thesis justice in that it is but a brief survey of extensive experimentation to establish ways and means of producing peritoneal immunity. Herrmann and others suggested that the exudate of peritonitis is a protective mechanism against the spread of bacteria and their toxins. He noted that if vaccination was seemingly complete, peritonitis did not appear. Similarly, varying gradations of vaccination resulted in varying amounts of fibrinous deposit and of exudation onto the peritoneum. David [2] also noted that when a transudate was formed in the peritoneal cavity of dogs, as by injection of hypertonic solution of dextrose, the absorption of diphtheria antitoxin was augmented, whereas in the presence of peritonitis, its absorption was decidedly retarded.

Métalnikov and Toumanoff,[3] by injecting bacterial cultures or carmine into the peritoneal cavities of guinea-pigs, found early response on the part of the microphages; the maximal response occurred in three hours, but the proportion of macrophages was highest on the third day after injection, and the proportion of lymphocytes was highest on the fifth day. Phagocytosis clearly was manifested earlier in vaccinated than in nonvaccinated animals.

Kittinger,[4] in twenty-six cases in which there was a gangrenous or perforated appendix and in two cases of strangulated hernia, in patients ranging in age from 4 to 86 years, poured from 50 to 150 cc. of colon bacilli and mixed culture filtrates into the peritoneal cavity after the necessary surgical procedure and made a primary abdominal closure. All of the patients lived.

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1. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, Arch. Surg., to be published.

2. David, V. C.: Peritonitis; an Experimental Study, Surg. Gynec. Obst. **45**:287, 1927. David, V. C., and Sparks, J. L.: The Peritoneum as Related to Peritonitis, Ann. Surg. **88**:672, 1928.

3. Métalnikov, S., and Toumanoff, K.: Réaction des cellules et phagocytose chez le cobaye normal et immunisé, Ann. de l'inst. Pasteur **39**:909, 1925.

4. Kittinger, Alois: Die Behandlung der eitrigen Peritonitis mit keimfreien Koli- und Mischkulturfiltraten (Antivirus), Wien. klin. Wchnschr. **40**:997, 1927.

Steinberg and Goldblatt,[5] in March, 1927, noted that after injection intraperitoneally of gum tragacanth and colon bacilli into animals, bacteremia did not occur, but peritonitis developed and death followed; with the injection of colon bacilli alone these organisms appeared in the lymph and blood stream. They interpreted these data as meaning that the peritonitis is the serious part of the process. Later experiments by them[6] (January, 1928) tend to show that subcutaneous vaccination against such peritonitis is as satisfactory as vaccination by the intraperitoneal route. Herrmann's work tends to refute this hypothesis, and he demonstrates clearly not only the importance of the intraperitoneal route of vaccination, but the greater importance of using a mixed culture of colon bacilli and streptococci isolated from the heart's blood of animals that have died of peritonitis.

As early as 1921, Draper[7] advocated the use of an antiserum against these two organisms. At the time of colectomy on patients at Trenton, he isolated streptococci and colon bacilli from the mesenteric lymph nodes of patients. Horses were immunized with these two bacteria, and patients were given from eight to ten injections of the horse serum over a period of a month with "definite decrease in mortality." In a recent personal communication, he stated that this work has not been continued.

Popesco-Combiesco[8] recently demonstrated that extracts of platelets injected into rabbits immunized against cholera vibrio prevented cholera peritonitis. Mikulicz attempted intraperitoneal vaccination with colon bacilli but because of severe reaction to the patient, abandoned the method after three or four attempts. One of us (F. R.) had suggested repeatedly that vaccination of patients against peritonitis before operations on the colon had great potential value. It remained but to work out methods. Herrmann's experiments seemed so clearcut that we felt justified in attempting a similar procedure in patients who were to have resections of the colon for malignant conditions. The first vaccine used was prepared from human fecal strains of colon bacilli and strep-

5. Steinberg, Bernhard; and Ecker, E. E.: The Effect of Antiserum Against the Soluble Toxic Substance of Bacillus Coli in Bacillus Coli Peritonitis, J. Exper. Med. **43**:443, 1926. Steinberg, Bernhard; and Goldblatt, Harry: Studies on Peritonitis: I. Production of Experimental Peritonitis and Survival Following Intraperitoneal Injection of Bacillus Coli, Arch. Int. Med. **39**:446 (March) 1927.

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7. Draper, J. W.: The Use of a Colon-Streptococcus and Anti-Serum as a Pre-Operation Measure, Proc. Soc. Exper. Biol. & Med. **19**:243, 1921-1922.

8. Popesco-Combiesco, Cornelia: Action préventive vis-a-vis de la péritonite vibrionienne expérimentale de l'extrait de plaquettes sanguines de lapins immunisés contre le vibrion cholérique, Compt. rend. Soc. de biol. **97**:1001, 1927.

tococci isolated from the heart's blood of these animals after mass feces had been instilled in their peritoneal cavities. Similar strains were isolated later from patients who died with peritonitis, and most of the patients whose cases form the basis of this report received vaccine prepared from these strains of human origin. Vaccines were prepared separately from each of these organisms, and later a mixed suspension in sodium chloride was made with a density of about 1,000,000,000 organisms for each cubic centimeter. The organisms were isolated by means of a blood agar plate, and after isolation they were grown in dextrose-brain broth (Rosenow) or pancreatic-digest broth. Twenty-five hundredths of a cubic centimeter of this vaccine made up to 1 cc. with physiologic solution of sodium chloride was given subcutaneously one week before the anticipated date of operation. If an unusual reaction

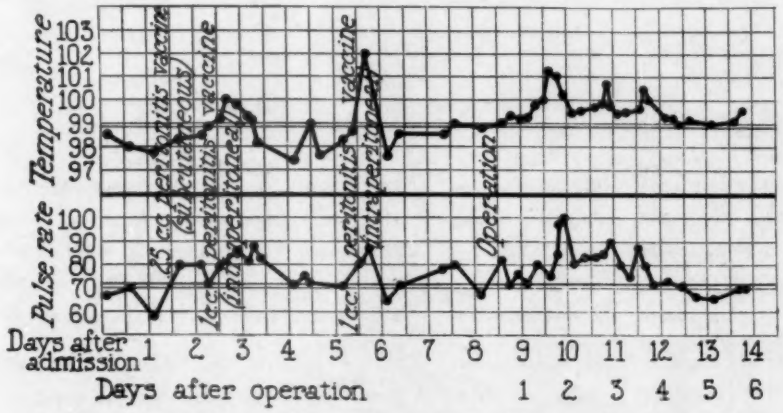

Chart 1.—Temperature chart of patient who had had two injections of intraperitoneal vaccine. Record for six days following ileocolostomy.

did not occur, 1 cc. of this vaccine in 10 cc. of the solution was injected intraperitoneally the next day. After an interval of two days, a similar injection was given; two days of rest followed, and then operation was performed.

Reactions following intraperitoneal injections all have been similar (charts 1 to 4); they are fairly severe and include rise in fever to as high as 103.5 F. within from two to four hours after the injection, diffuse abdominal soreness and tenderness, short jabbing abdominal pains, some distention, occasional chills and an invariable general leukocytosis. In from twelve to twenty-four hours this reaction subsides, a feeling of general well being prevails and often the entire blood picture improves.

The reaction from the second injection is almost invariably lighter (table 1).

Three of the sixty patients who received this vaccine in the manner described, together with the other preoperative measures described elsewhere, and who underwent the various surgical procedures (table 2) were found at necropsy to have had peritonitis. These three do not

TABLE 1.—*Reaction to Vaccine*

	Before Vaccine			After Vaccine			
Case	Hemoglobin, Per Cent	Erythrocytes, Millions	Leukocytes, Thousands	Hemoglobin, Per Cent	Erythrocytes, Millions	Leukocytes, Thousands	Temperature, F.
1	65	3.58 *	10.6	73	4.72	14.2	103.0
2	48	3.15	6.6	60	3.92	13.2	101.5
.	..	....	...	..	....	10.0	102.0
3	40	2.76	7.6	40	3.09	16.9	101.0
4	46	....	7.2	65	.. .	15.6	101.2
5	65	3.88	11.6	80	4.24	17.3	101.0
6	79	4.59	10.6	83	5.00	13.5	100.5
7	65	3.80	8.8	75	4.52	14.5	101.2
8	76	4.22	11.2	78	4.70	18.6	103.0
9	53	3.71	4.5	68	4.19	6.6	102.5

* Ileocolostomy

TABLE 2.—*Operations After Treatment by Vaccine*

Patients	Lesion	Site	Surgical Procedures
5	Carcinoma	Cecum	First stage, ileocolostomy; second stage, hemicolectomy
4	Carcinoma	Ascending colon	First stage, ileocolostomy; second stage hemicolectomy
3	Carcinoma	Hepatic flexure	First stage, ileocolostomy; second stage, hemicolectomy
1	Sarcoma	Hepatic flexure	First stage, ileocolostomy; second stage, hemicolectomy
6	Carcinoma	Transverse colon	Obstructive resection (first and second stage Mikulicz)
1	Carcinoma	Transverse colon	Exploration
2	Carcinoma	Transverse colon	First and second stage Mikulicz and appendicostomy
1	Carcinoma	Transverse colon	First and second stage Mikulicz and partial gastrectomy
1	Carcinoma	Splenic flexure	First and second stage Mikulicz
1	Carcinoma	Splenic flexure	Colostomy
1	Carcinoma	Descending colon	First and second stage Mikulicz
1	Carcinoma	Descending colon	Colostomy and aseptic resection with anastomosis over Rankin clamp
1	Carcinoma	Descending colon	First stage, colostomy; second stage, resection
1	Carcinoma	Sigmoid colon	Obstructive resection
3	Carcinoma	Sigmoid colon	First stage, colostomy; second stage, anterior resection with anastomosis
2	Carcinoma	Sigmoid colon	Exploration
1	Carcinoma	Sigmoid colon	Cecostomy, resection, and anastomosis
13	Carcinoma	Rectosigmoid colon	Procedures included: combined abdominoperineal resection and colostomy; colostomy and resection; cecostomy, resection and anastomosis, and first stage, colostomy; second stage, resection
9	Carcinoma	Rectum	First stage, colostomy; second stage, posterior resection
1	Carcinoma	Ileum	Resection and end-to-end anastomosis
1	Malfunctioning ileocolostomy and cecosigmoidostomy	Sigmoid colon	Cutting off and repairing
1	Chronic ulcerative colitis	Colon	Exploration and biopsy

embrace the total mortality in this group of cases, but it is noteworthy that in only three cases was there fatal peritonitis.

In the control group of sixty cases the lesions were located in the same segments of the colon as those in which the lesions were found

in the group which received vaccine, and the patients were operated on under the same conditions by the same surgeons. Of these fourteen died, a mortality of 23 per cent as against 5 per cent in the vaccinated cases.

The lowering of the mortality by 18 per cent in this series, while perhaps not attributable entirely to the vaccine, recommends it as a likely factor. The ages of the patients who received vaccine were as follows: four in the fourth decade, fourteen in the fifth decade, eighteen in the sixth decade, thirteen in the seventh decade and six in the eighth decade. The ages of the patients who did not receive vaccine were: seven in the fourth decade, fifteen in the fifth decade, seventeen in the sixth decade, fifteen in the seventh decade and six in the eighth decade.

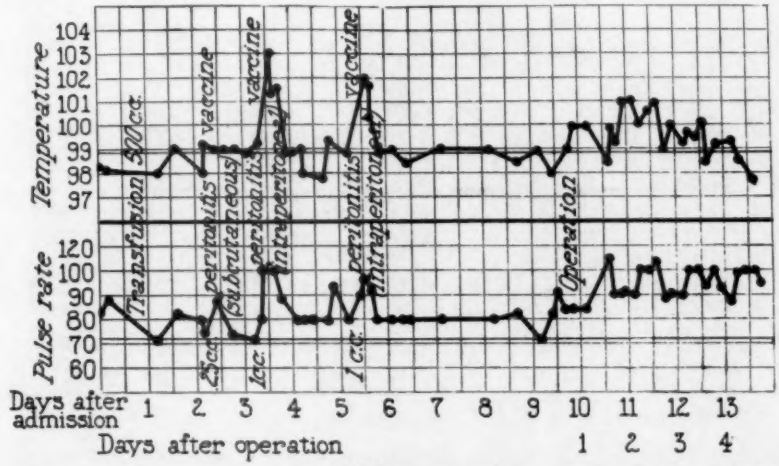

Chart 2.—Temperature chart of patient who had had two injections of intraperitoneal vaccine. Course following first and second stage Mikulicz operation for obstructive carcinoma of the transverse colon.

Postoperative reactions, as measured by a rise in temperature, were greater in the nonvaccinated than in the vaccinated group. With the exception of one case in which the temperature rose to 105 F., the highest fever attained in the vaccinated group was 103 F. The average duration of fever after operation in the vaccinated cases, including three cases in which fever persisted for eighteen, nineteen and twenty days, respectively, was four and nine-tenths days. In several cases the maximal rise of temperature after resection was as low as 99.5 F. With the exception of one case in which the temperature rose to 106 F., the highest fever attained in the unvaccinated group was 105.5 F. The latter temperature occurred in several cases. In several cases the low level of 101 F. was attained as the maximal rise in temperature after resection. The average duration of fever after operation in the

group of cases in which vaccine was not given, omitting one case in which fever persisted thirty-five days, and another in which it continued for many weeks, was ten days. The groups include patients with lesions of all parts of the colon and rectum, one patient with carcinoma of the ileum and several patients who underwent resections for mechanical or adhesive obstruction.

There were seven patients with carcinoma of the cecum, four with carcinoma of the ascending colon, three with carcinoma of the hepatic flexure, one with sarcoma of the hepatic flexure, ten with carcinoma of the transverse colon, two with carcinoma of the splenic flexure, three with carcinoma of the descending colon, nine with carcinoma of the sigmoid, twelve with carcinoma of the rectosigmoid, six with carcinoma of the rectum, one with carcinoma of the ileum, one with a

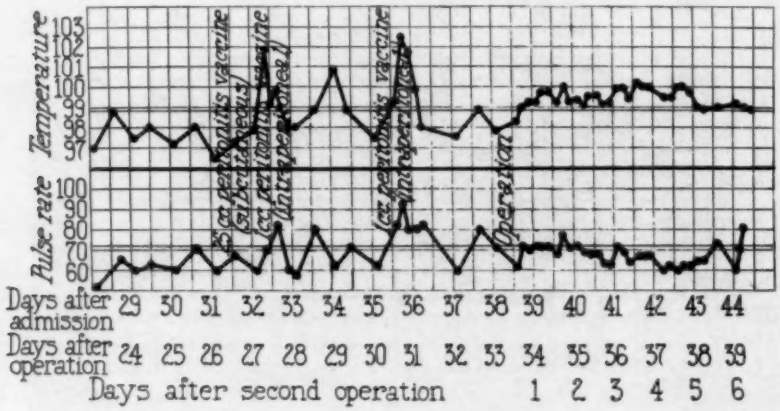

Chart 3.—Temperature chart of patient who had had colostomy and combined anterior and posterior resection for rectosigmoidal carcinoma after two injections of intraperitoneal vaccine.

malfunctioning ileocolostomy and cecosigmoidostomy, and one with chronic ulcerative colitis.

The group of patients who died following resection of the colon, after having had intraperitoneal vaccination, was small. Although the three cases which we discuss briefly do not represent the whole mortality in this series, they represent the total mortality among those patients who had peritonitis.

One patient, a man, aged 40, had an ileocolostomy for carcinoma of the cecum and ascending colon and died on the twelfth day from general peritonitis and ileus. This man had a large, fixed tumor of the cecum which was adherent to the abdominal wall. The advisability of resecting this tumor at a subsequent stage was questionable because of its immobility. An aseptic anastomosis was carried out satisfactorily, and we believe that peritonitis came from the exploration of the growth.

The second case was that of a man, aged 31, with a colloid carcinoma of the rectum, on whom a combined abdominoperineal resection was performed in one stage. He died seven days later, with general peritonitis and pelvic cellulitis.

In the third case, there is a question as to the accuracy of the diagnosis of cause of death. This patient was a man, aged 68, who had carcinoma of the transverse colon for which a temporary colostomy proximal to it was done. He died seven days later, and it was found that he had exudative peritonitis, but he also had marked myocardial degeneration and arteriosclerosis graded 3. The postoperative convalescence was entirely uneventful until the sixth day, when he suddenly went into collapse with some pain in the chest, dyspnea, cyanosis and a thready, rapid pulse which led us to believe he might be the victim

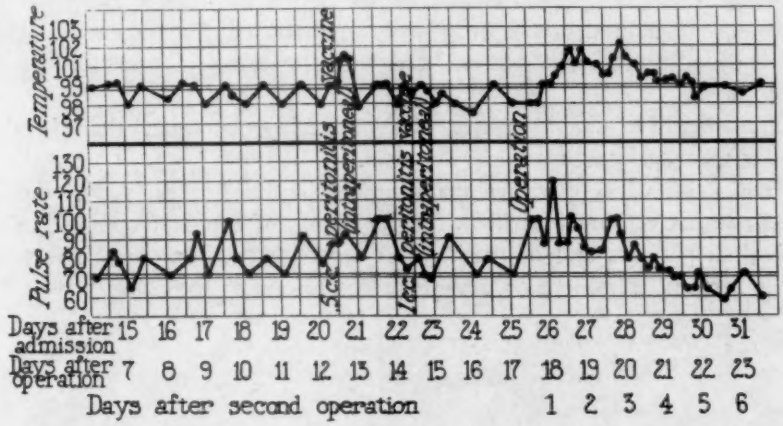

Chart 4.—Temperature chart of patient who had had resection of the right colon following injection of intraperitoneal vaccine. Rapid return to normal of pulse and temperature is shown.

of pulmonary embolus. He died twelve hours later. We count this death as one of peritonitis following colostomy, but believe that it is extremely doubtful whether the peritonitis actually was the cause.

Another case in this series in which the patient died is recorded because of the fact that a secondary operation for obstruction was necessary seven days after the resection, and at that time the abdomen was entirely free from any infection or contamination. This patient was a woman, aged 47, who had had a rectosigmoidal carcinoma and on whom a combined two-stage abdominoperineal resection had been performed. The colostomy was done on July 23; the resection, on Aug. 9, 1928. The first day following resection, ileus developed and enterostomy was performed. A loop of small bowel was found to be hugely distended and obstructed from adhesion into the pelvis. Enterostomy for acute intestinal obstruction was then performed. It was

noted that the peritoneal cavity was clear of any infection, and it was felt that relief from obstruction would prove life saving; however, the patient died eight days later, and peritonitis was found at postmortem examination. Unquestionably, this peritonitis came from the enterostomy.

Table 2 shows types of operations performed after patients had been vaccinated and had received other preoperative care. The procedures employed in cases of patients who did not have vaccine were similar, although in a number of instances operations thought to be accompanied by less risk were employed.

CONCLUSIONS

Intraperitoneal vaccination with colon bacilli and streptococci, as an adjunct to other preoperative measures, seems a valuable asset in the treatment of patients with malignant growths of the colon. In this series of sixty cases, there was a definite lowering of mortality from peritonitis.

Postoperative convalescence was noticeably smoother than in the similar group of cases used as controls.

The value of cooperative management in these cases is well established, and selection of patients for operation, of types of operation for individual patients and of methods of anesthesia are important factors in the surgical treatment of malignant conditions of the colon.

ACUTE OBSTRUCTION OF THE SMALL INTESTINE DUE TO A GALLSTONE

RECOVERY FOLLOWING OPERATION *

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Intestinal obstruction due to a large gallstone impacted in the lumen is rare enough to occasion considerable interest. The early recognition of the condition is of especial importance because of the dangers of delay in operation.

Courvoisier,[1] in 1890, collected 131 cases of obstruction due to a gallstone. Wagner [2] found a total of 334 cases on record in 1914.

In a study of 3,064 cases of intestinal obstruction, reported from seven hospitals in 1925,[3] there were only 28 due to a gallstone. The most frequent causes were hernia, intussusception, carcinoma, adhesions, internal strangulation and volvulus.

The age at which obstruction from a gallstone usually occurred was between 50 and 70 years. It was more common in women, in whom the incidence was 191, than in men, in whom it was 71 (Wagner).

Gallstones may gain access to the intestinal tract by perforation from the gallbladder or by entrance from the common duct.

In 36 cases studied, Courvoisier found a fistula from the gallbladder into the duodenum in 25, into the ileum in 1, and into both the duodenum and the colon twice. In the remaining 7 cases, the gallstone evidently entered through the choledochus.

Perforation from the gallbladder may follow a primary inflammation with attachment to a viscus or the inflammation may start in the latter, as from a perforating ulcer of the duodenum.

Courvoisier described fistulas between the gallbladder and the pleura, the lungs, the female genitals, and passage of gallstones from the urinary bladder.

The site of incarceration of the gallstone is usually in the terminal ileum because of its small lumen. Hermann [4] found in 145 cases that

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* Submitted for publication, March 2, 1929.

1. Courvoisier, L. G.: Beitrage zur Pathologie und Chirurgie der Gallerwege, Leipzig, 1890, p. 101.

2. Wagner, Arthur: Ileus durch Gallensteine, Deutsche Ztschr. f. Chir. **130**:353, 1914.

3. Report from Annual Meeting of the British Medical Association, Brit. M. J. **2**:993 (Nov. 18) 1925.

4. Hermann, quoted by Wagner.

the point of obstruction was in the colon in 13 cases, the duodenum in 9, the jejunum in 30 and the remainder in the small intestine, chiefly the terminal portion.

Wagner reported a fatal case in which two separate perforations from the gallbladder into the duodenum were followed by attacks of ileus fifteen days apart, and operative removal of the gallstone during each attack.

Unusually large gallstones have reached the terminal ileum before incarceration. Rankin and McKeith [5] reported one measuring 6.9 by 8.5 cm., Clement [6] found one gallstone measuring 2½ by 1¼ inches (6.3 by 3.1 cm.). Bennett [7] removed one at operation with the greatest circumference of 5½ inches (14 cm.) and weighing 636 grains (41.3 Gm.).

Large gallstones have passed spontaneously after severe symptoms of ileus. Coldren [8] reported one 2 by 1 inches (5 by 2.5 cm.) in diameter, which passed after severe obstructive symptoms for one week, with recovery. A volvulus of the small intestine occurred above the gallstone obstruction in a case reported by Smith.[9]

The onset of symptoms is usually acute, with severe colic, persistent pain and vomiting. Moore [10] observed that the pain may be more on the left side. Visible peristalsis may be observed. The vomitus usually contains bile at first, and then becomes fecal with the development of tympanites and other evidence of obstruction. The condition of the patient is usually good for the first few days.

Wagner stated that one may occasionally palpate the gallstone. Bonnecaze and Le Chaux [11] stated that a tumor may be felt with the patient under anesthesia, and that the symptoms of obstruction may be mild but persistent.

A roentgenogram of the abdomen may show distention of the small intestine, characteristic of obstruction, with the shadow of the gallstone, as in the case reported. Displacement of the colon may result from the distended loops of intestine. As a means of localizing the obstruction

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5. Rankin, F., and McKeith: Gallstone Ileus, Kentucky M. J. **22**:236 (July) 1924.

6. Clement, G. H.: Intestinal Obstruction Due to Gallstones, Canad. M. A. J. **11**:262 (April) 1921.

7. Bennett, Charles: Obstruction of Small Intestine by Gallstones, Brit. M. J. **1**:565 (March 27) 1926.

8. Coldren, R. S.: Intestinal Obstruction by Gallstone, Brit. M. J. **1**:783 (May 1) 1926.

9. Smith, N. R.: Acute Intestinal Obstruction Due to a Gallstone, Brit. M. J. **2**:479 (Sept. 12) 1925.

10. Moore, G. A.: Gallstone Ileus, Boston M. & S. J. **192**:1051 (May 28) 1925.

11. Bonnecaze, J., and Le Chaux, A.: Arch. d. mal. de l'app. digestif **14**:201 (March) 1924; abstr., J. A. M. A. **82**:1821 (May 31) 1924.

in the small or large intestine, it may be advisable to use the roentgen rays following a barium enema. Although the symptoms may be suggestive, the diagnosis has rarely been made before operation.

The prognosis is good with early operation, since there is rarely early strangulation of the obstructed intestine. However, the mortality rate has always been high, due to late operation. Fourteen of twenty-eight cases were fatal.[3]

The treatment is immediate operation. Usually removal of the gallstone and closure of the intestine is all that is necessary. An enterotomy was done in twenty-five of twenty-eight cases, and an enterostomy in three.[3]

REPORT OF CASE

History.—J. D., a woman, aged 63, complained of acute pain in the epigastrium, vomiting, loss of appetite and some fever.

The onset began with sharp pains in the epigastrium one week before admission to the hospital. They were somewhat intermittent, but had been worse the previous night. There was radiation of the pain to the back. Nausea was severe with some vomiting of dark, bitter material increasing in severity the last two days.

There had been two previous similar attacks of pain, one fifteen years ago, and another, a year ago. There had been numerous mild attacks of pain and discomfort especially during the last year. The patient had never been jaundiced.

The bowel movements had been regular, with slight constipation the last two months. There were no clay-colored stools. The appetite was usually good. The patient had never noted that any special food caused distress. On admission to the hospital, she weighed 233 pounds (105.7 Kg.), showing a gain of 40 pounds (18.1 Kg.) in the last six months.

The patient had passed five or six small stones from the bladder, some during the last year. There was an occasional slight burning on urination, but no hematuria.

She had had pneumonia eighteen years ago, and had had smallpox when a child. There was no history of typhoid. An operation had been performed three years ago when the uterus was removed for a tumor.

She had had two children, both of whom were living and well. Her father died at 76 years of age with kidney trouble, and her mother at 76 with heart trouble. She had five brothers, who were well, and three sisters, who were dead.

Examination.—The woman was very obese and did not appear acutely ill. The abdomen was prominent and fat. Tenderness with some muscle spasm and rigidity was present over the region of the gallbladder, but no mass was palpable. The abdomen was not distended with gas. Otherwise the results of the examination were negative.

The pulse rate was from 96 to 108. The temperature was 100 F., increasing a little during three days of observation in the hospital.

The blood count showed: white blood cells, 11,800; hemoglobin, 70 per cent; red blood cells, 4,780,000. The blood pressure was 120 systolic and 58 diastolic. The urine was normal, except for a trace of albumin on the second day. An Ewald test-meal demonstrated free hydrochloric acid, 35; total acid, 40. The stools were negative. The van den Bergh test of the blood was negative on both the direct and the indirect reactions.

A roentgenogram of the region of the gallbladder showed a small spherical, dense shadow with a faint oval shadow about it (fig. 1 *A*). The roentgenologic diagnosis was that the outer fainter shadow was due to a thickened, enlarged gallbladder containing a stone, as shown by a central denser shadow. Roentgenograms of the kidneys were negative. There was a small area of density in the pelvic region suggesting a bladder stone.

The increasing severity of the symptoms with vomiting, and the roentgen observations, made it seem advisable to operate without further delay.

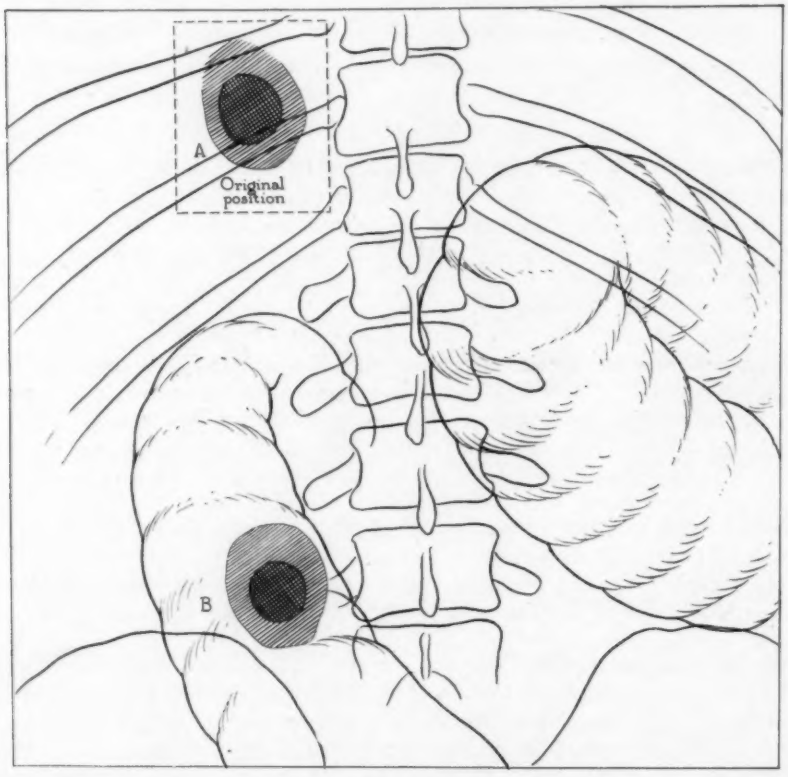

Fig. 1.—The insert *A* was made from a roentgenogram taken two days before operation. It shows the shadow of the suspected gallstone over the region of the gallbladder. The more dense central area was thought to be a gallstone, while the outer area of density resembled an enlarged thickened gallbladder. *B*, made from a roentgenogram taken eight days following operation, shows that the shadow had shifted downward. At a second operation a huge gallstone was found impacted in the terminal ileum, with complete intestinal obstruction. Several markedly dilated loops of small intestine are clearly shown in the roentgenogram.

First Operation.—Ethylene with some ether was given. The abdomen was explored as well as possible, considering the obesity. No abnormalities, apart from the gallbladder region, were found. The intestines were not distended, and the pancreas was normal. There was an acute inflammatory mass over the region

of the gallbladder formed by adhesions of the omentum to the liver and duodenum. This mass was hard and edematous, resembling a malignant induration.

The omentum was carefully separated from the liver, and a small friable, thickened gallbladder was opened. The first portion of the duodenum was found to be intimately adherent to the gallbladder with extensive inflammatory tissue. When they were separated, a large opening was observed over 4 cm. in diameter in the duodenum, freely discharging bile and a lacerated opening along the lower side of the gallbladder. Owing to the extensive adhesions and inflammation, the existence of a perforation before separation of these viscera could not be definitely

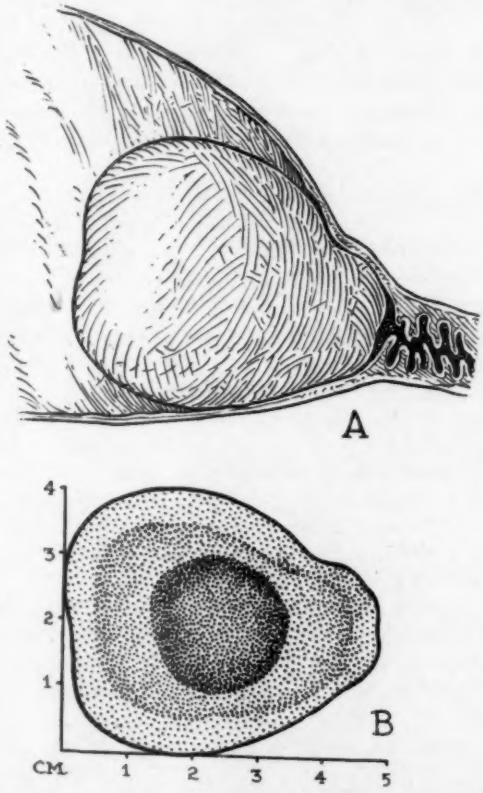

Fig. 2—*A* illustrates the large gallstone completely impacted in the terminal ileum. *B* was drawn from a roentgenogram of the gallstone after removal. It shows a dense central shadow and an outer lighter zone with two or three slightly shaded concentric layers. The stone measured 4 cm. by 4.8 cm. in diameter.

determined. The hole in the duodenum was closed transversely with layers of catgut and silk and covered with omentum.

The gallbladder was thickened, friable and severely lacerated. The cystic duct was narrowed and edematous. It admitted only a fine probe. The opening was enlarged, and the enlarged common duct was probed and palpated. The bed of the gallbladder in the liver was then searched for a gallstone, but none was found. Since the flow of bile from the common duct into the duodenum was not obstructed, and since the patient was not a good risk, due to her age and obesity,

no further exploration was done. The gallbladder was removed and the opening in the cystic duct closed with catgut. Drainage tubes were inserted and the abdomen was closed.

Postoperative Course.—For the first few days following the operation, convalescence was not unusual, although vomiting frequently occurred with small amounts of liquids. The stomach was washed, but vomiting persisted. After the first few days the stomach was washed more frequently, but gastric retention still persisted. On the sixth postoperative day, the gastric contents were observed to be foul smelling and of a brownish color. The stomach was washed every four hours day and night for the next two days. On the seventh day, there was copious drainage of bile from the wound and the amounts obtained from aspiration of the stomach were much lessened. On the eighth day, the patient seemed considerably weaker, and distention of the abdomen was noted for the first time.

During the entire postoperative course, plenty of fluids were given subcutaneously and by rectum. There had been little abdominal pain or complaint following the operation.

A roentgenogram of the abdomen was taken on the eighth postoperative day. There was a spherical shadow similar to that seen in the region of the gallbladder but it was now considerably lower on the right side, in the angle between the lumbar spine and the crest of the ilium (fig. 1 *B*). Distention of several loops of small bowel with gas, with widest measuring about 8 cm. was plainly seen. The stomach and colon were not distended. A diagnosis of obstruction of the terminal ileum by a gallstone was made.

Second Operation.—The second operation was done at once under local anesthesia. The region of the previous operation was prepared and walled off carefully, and the incision was made to the left of the umbilicus. Moderate distention of the jejunum and ileum with gas was present, with but little fluid content. The duodenojejunal angle was located and the intestine followed down until within 1 or 2 feet of the terminal ileum. Here the distended bowel terminated suddenly, due to a large gallstone, which was tightly impacted in the lumen. The bowel was completely collapsed below it (fig. 2 *A*).

A longitudinal incision was made and the gallstone removed. The intestine was not gangrenous and the opening was closed transversely with catgut and fine silk. There was a small amount of turbid exudate in the peritoneal cavity, but the region of the liver and bile ducts was not disturbed. Closure was done without drainage.

Postoperative Course.—Convalescence was uneventful and bile drainage stopped after ten days.

The microscopic sections of the gallbladder showed an acutely inflamed, greatly thickened wall. The gallstone was black and moderately soft on the surface. It measured 4 cm. by 4.8 cm. A roentgenogram of this stone showed a central spherical dense shadow and an outer, more oval lighter shadow (fig. 2 *B*). Several concentric outer layers were evident in this film, but not in those taken of the abdomen.

COMMENT

It is probable that the gallstone perforated shortly before the first operation, since the roentgenogram taken two days before showed the shadow in the region of the gallbladder. Vomiting and retention, which developed that day, were probably the result of the entrance of the large stone into the upper intestine. However, the stone probably did not

produce complete obstruction until the eighth postoperative day. Then it became completely impacted in the lumen of the narrow terminal ileum, and tympanites developed.

A roentgenogram was then taken of the abdomen, which showed marked distention of the small intestine and downward displacement of the shadow of the gallstone. This permitted a correct diagnosis.

At the first operation, the gallstone was thought to be only the central dense shadow surrounded by a thickened gallbladder, giving a faint shadow. There was no indication to strip the small intestine before exploring the indurated mass about the gallbladder, since there was no distention of the intestine. After the opening in the duodenum was closed, the bile ducts explored and the severely lacerated gallbladder removed, the condition of the patient did not justify prolonging the operation in further search for the gallstone.

The shadow interpreted in the first roentgenogram as the gallstone was only the denser core, which was apparently small enough to pass through the intestine. If it had been possible to determine that such a large gallstone had already perforated into the duodenum it would have been preferable to find and remove it without disturbing the inflammatory mass about the gallbladder.

CONCLUSIONS

1. A gallstone as a cause of intestinal obstruction should be considered with symptoms of inflammation of the gallbladder followed by those of intestinal obstruction.

2. Roentgenograms may show characteristic evidence of intestinal obstruction together with the shadow of the gallstone.

3. Early operation should be performed.

A REVIEW OF UROLOGIC SURGERY*

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KIDNEY

Anomalies.—Kimbrough [1] reported a case of carcinoma of a horseshoe kidney occurring in a man, aged 35 years. Cystoscopic examination did not show anything of a pathologic nature in the bladder. A specimen from the left ureteral orifice was bloody, and one from the right was clear. Catheters were passed to the pelvis of the kidney without difficulty. A pyelogram revealed that the right ureter entered the pelvis laterally and was somewhat dilated. The calices pointed toward the median line and the pelvis was dilated. The left kidney was over the third and fourth lumbar vertebrae. During general examination a palpable mass was felt in the left side of the abdomen above the crest of the ilium. The mass was smooth, firm and slightly movable, and was posterior to the descending colon. It had an excursion of 1 cm. with respiration. The preoperative diagnosis was congenital anomaly, probably fused kidney.

At operation a large, fairly solid-feeling, smooth, walled-off mass about 10 cm. in diameter was exposed behind the posterior peritoneal layer, reaching upward under the ribs on the left side and over and across the median line below the stomach. The outer leaflet on the mesocolon of the descending colon was incised and the tumor exposed through this opening. The mass was dense and connected with the opposite kidney at the lower and inner portion by an isthmus of renal tissue. After considerable difficulty the tumor was exposed, and the pedicle and ureter were doubly clamped and divided. The isthmus

* Submitted for publication, Aug. 23, 1929.

1. Kimbrough, J. C.: Carcinoma of a Horseshoe Kidney, Mil. Surgeon **64**: 91, 1929.

was divided and the left kidney was delivered. The kidney measured approximately 17 by 11 by 10 cm. The pathologic diagnosis was papillary adenocarcinoma.

[COMPILERS' NOTE.—Pathologic changes are more common in horseshoe kidneys than in the usual type of kidneys. Obstruction, infection and stone result from inefficient ureteral drainage. The formation of tumor, which is comparatively common in horseshoe kidney, apparently results from the same causes. Hellsten [2] found eight tumors in 107 cases of operative horseshoe kidney. Morley [3] reported a case of papilloma of the renal pelvis causing hydronephrosis. Wolff [4] reported a case of hypernephroma with extensive metastasis, even in the opposite renal segment. Haas [5] described an unusual case in which the resected right kidney showed three different types of renal tumor. A hypernephroma about 8 cm. in diameter was found in the upper pole, an adenoma about 3 by 5 cm. was found in the lower third, and a small papilloma was found in the lower division of the pelvis. Several more recent cases of squamous cell tumors associated with calculi have been reported. In most of the published reports the cases are unusual in that the tumors are generally found in the right division of the horseshoe mass.]

Campbell [6] presented a clinicopathologic study of nine cases of complete unilateral agenesis of the kidney found in 13,000 necropsies at Bellevue Hospital and one case presumably of this character observed clinically. In a series of 122,320 necropsies which Campbell reviewed, he found an incidence of one case of unilateral renal agenesis in 1,610 cases.

Clinically, apparent pathognomonic signs or symptoms of unilateral kidney are not present, and the condition is usually not suspected during life. The diagnosis is often not made until operation. Ransahoff stressed the surgical import of this condition; in 1912, he reviewed eleven cases in which, unknowingly, the only kidney had been removed or was otherwise surgically incapacitated. All the patients died promptly of uremia. Age is a factor of comparatively little importance. A person whose kidney is congenitally absent may expect as long a span of life as that for many patients on whom nephrectomy has been

2. Hellsten, O. T.: A Case of Hydronephrosis in a Horseshoe Kidney: Heminephrectomy, Acta chir. Scandinav. **59**:415, 1925-1926.

3. Morley, John: Case of Papilloma Causing Hydronephrosis in a Horseshoe Kidney, Lancet **1**:1617, 1910.

4. Wolff, T. R.: A Case of Hypernephroma in a Horseshoe Kidney, Am. J. Urol. **8**:627, 1912.

5. Haas, N. C.: Tumoren in Hufersennieren, Ztschr. f. Urol. **19**:81, 1925.

6. Campbell, M. F.: Congenital Absence of One Kidney: Unilateral Renal Agenesis, Ann. Surg. **88**:1039, 1928.

performed. Campbell noted, however, that in a third of the cases of this series that came to necropsy the patients died of renal failure.

Renal vessels were not found in seven of the series, and in two instances their presence was not recorded. In a series of thirty-nine cases of renal aplasia which Campbell reported elsewhere, a few were of degenerative type and unquestionably would be overlooked unless the atrophic vascular supply gave a clue. There was evidence of ureteral budding in only one of Campbell's cases. A fibrous thread left the bladder at the normal exit but was lost in the lumbar retroperitoneal fat. In none of his cases was a ureteral opening present on the affected side; dimpling was seen in four cases. Aplasia or agenesis of genital and reproductive organs is occasionally associated with renal agenesis. A unicorn uterus with rudimentary ovary and fallopian tube was found in two instances. In another case, the testicle on the involved right side was retroperitoneal and atrophic. The right seminal vesicle and vas deferens were also atrophic.

The solitary kidney must often bear an exceedingly heavy burden; in three of the cases a destroyed kidney was found at necropsy. In one case there was generalized infarction, in one case, acute suppurative focal nephritis, and in another case, a typically scarred kidney of chronic interstitial nephritis. All the patients died of uremia.

[COMPILERS' NOTE.—Attention is called again to the importance of bilateral renal investigation, if a surgical procedure on the kidney or ureter of one side is contemplated. Although the differentiation of solitary kidney and renal aplasia, atrophic pyelonephritis and occluded renal tuberculosis may be difficult, the practical point which can be demonstrated is that one kidney does not function. If this is demonstrated, it is sometimes necessary to change the character of the treatment of disease on the side which is carrying on the function.]

Hennessey [7] reported a case of congenital solitary kidney. Three hundred seventy-two cases of congenital absence of the kidney have been reported in the literature. The frequency of this anomaly as indicated by necropsy reports is about one in 1,000 cases. The presence of two ureteral orifices does not always indicate that there are two kidneys. A ureteral orifice on the side of the renal aplasia was found in about 10 per cent of the cases. Associated genital anomalies occurred in about 33 per cent of the cases. The presence of genital anomalies should arouse suspicion of urinary dysplasia.

Pyelitis of Pregnancy.—Hofbauer [8] stated that the cause of urinary obstruction in pregnant women is due to certain anatomic conditions

7. Hennessey, R. A.: Congenital Solitary Kidney, J. Urol. **21**:193, 1929.

8. Hofbauer, J. I.: Studies on the Etiology and the Treatment of Pyelitis in Pregnancy, New England J. Med. **198**:427, 1928.

in the portion of the ureter close to the bladder and in the trigonum vesicae. Hypertrophic changes in the musculature, associated with hyperplastic changes in the connective tissue, are essential factors in the narrowing of the lumen of the lower part of the pelvic portion of the ureter. The constriction is accentuated by an encircling ring resulting from hypertrophy of the ureteral sheath, and engorgement of the vessels in the mucosa and dextrorotation of the uterus may act as contributory factors.

It is common for pregnant women to have a moderate degree of hydro-ureter. The distal end of the ureteral dilatation usually lies at the level of the parametrium, the visible dilatation being associated with demonstrable delay in ureteral action. The hypertrophy of the trigonum accounts for the clinical phenomenon of residual urine in pregnant woman. Pugh noted that, in 100 apparently normal pregnant women examined between the seventh and ninth months of pregnancy, the ureters were sluggish in their action in 80 per cent of the cases. In practically every instance there was ureteral retention, mostly on the right side.

In six of fifty-five cases it was shown that there was definite lowering of the immunization power of the blood to the colon bacillus during pregnancy.

Histologic studies tend to substantiate the occurrence of involution processes within the ureteral wall, in analogy with the phenomena occurring in the uterus during the puerperium. Although after labor there is a gradual return of the renal pelvis and of the ureter to normal in uncomplicated cases, persistence of bacteria and of marked dilatation of the ureter is demonstrable in many women who had been treated for pyelitis during a preceding pregnancy. In the majority of these cases, the level above which the ureter has remained dilated corresponds to the parametrium. Stricture of the ureter may occasionally result from long-standing infection in the wall of the ureter during pregnancy.

Phaneuf [9] stated that, clinically, pyelitis of pregnancy is frequently encountered in the average obstetric case, because of the high temperature usually accompanying the lesion and the subsequent reference of these patients to the hospital. In his experience the mortality in this condition is low; deaths were not recorded at the Carney Hospital. It has been his practice to use conservative treatment, almost ultraconservative in most cases. Lately the use of the indwelling catheter has been recommended to drain the ureter and the pelvis of the kidney. The value of this method is emphasized by the etiology, for it dilates the constricted area caused by the hypertrophy of the periureteral sheath.

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9. Phaneuf, L. E.: Discussion, New England J. Med. **198**:437, 1928.

Irving [10] reported that of 9,209 pregnant women, 204 had pyelitis, an incidence of about one in forty-five. In seven of the 204 patients, it was advisable to terminate pregnancy. The other patients recovered as the result of treatment which included the use of urinary antiseptics, rest in bed and forced fluids, or cystoscopy.

Crabtree,[11] during the last seven years, at the Boston Lying-In Hospital, has not known a case of pyelitis of pregnancy in which recovery from infection has taken place during pregnancy. Occasionally the urine cleared to bacilluria which persisted throughout pregnancy. In some instances, especially in the last weeks of pregnancy, the urine may become cloudy again and symptoms of fever recur. This is attributed to change of position of the fetus preceding the onset of delivery. Acquired immunity doubtless protects these patients and allows them to throw off the remnants of infection after the acute symptoms have subsided. If patients have acute symptoms, the contents of the pelvis are considerably greater then than during the quiet stages of the disease previous to delivery. Bacilluria occurs frequently in pregnancy. In 200 cases of pregnancy, bacilluria was found in thirty-two.

Crabtree advised early cystoscopy as treatment of pyelitis of pregnancy, in the belief that reduction of overdistention and the clearing of a pelvis clogged with pus definitely hasten recovery.

[COMPILERS' NOTE.—The etiology of pyelitis of pregnancy has provoked much comment during the last few years. Carson, Pugh, and Corbus and Danforth have dealt intensively with the causal and therapeutic factors.

Stasis from organic changes in the ureteral musculature, from vascular engorgement, and from change in the anatomic relationships of the trigone, as well as the frequently lowered resistance of the patient to infections from the colon bacillus during pregnancy, has been the feature most often emphasized.

The fact has been established that pregnancy is associated with definite dilatation of the pelvis and ureter, which subsides to a greater or less degree during the first few months after the puerperium. Furthermore, it has been shown that a certain amount of residual pelvic and ureteral dilatation persists in most cases and thus renders the soil favorable for further infection, especially when the next pregnancy ensues.

The question of stricture as a result or as a cause of pyelonephritis of pregnancy is most elusive so far as its establishment as a pathologic fact is concerned. Corbus and Danforth stated that stricture is commonly associated.

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10. Irving, F. C.: Discussion, New England J. Med. **198**:439, 1928.

11. Crabtree, E. G.: Discussion, New England J. Med. **198**:437, 1928.

Unquestionably treatment with diuretic and urinary antiseptic drugs must be of value in the hands of the average practitioner. Nevertheless there is a growing tendency not to expect too much from medical treatment or to continue it too long. The institution of cystoscopy with repeated renal lavage or permanent drainage by catheter is generally recognized as a better mode of treatment. The indwelling catheter occupies a questionable position in the minds of some urologists who believe that the prolonged employment of large catheters incites a form of ureteritis which may in itself be dangerous. However, accidents with the method are clinically rare, and there are increasing numbers of advocates of the large indwelling catheter as the ideal method of treatment for this distressing type of infection of the urinary tract.]

Seng [12] observed that, in pregnancy, there is constant rightsided ureteral dilatation, whereas hydronephrosis on the right side is only slightly less common. The left ureter and renal pelvis are not affected in a high percentage of cases. Bilateral hydro-ureter and hydronephrosis are common. In the multiparous woman these conditions occur earlier, more commonly, and in more marked degree than in the primipara. The inability of the renal pelvis and ureter to empty themselves within the normal time limits is an almost universal observation in the antepartum woman. Stasis persists in the postpartum woman but in a lesser degree over a prolonged period. In the apparently healthy pregnant and puerperal patient there is probably renal complication in the presence of pus and coliform organisms.

Tumor.—Kretschmer and Doehring [13] stated that adenoma of the kidney is usually small, that it does not present clinical symptoms, and that it occurs most often in kidneys affected with interstitial nephritis. They reported a case of large benign adenoma, in which the kidney was removed and the patient was well without recurrence four years after operation.

The one constant symptom noted in a group of seventeen cases reviewed by Kretschmer was the presence of an abdominal tumor. Blood in the urine occurred in eight cases, pain in six cases and anemia in three cases. The tumor was on the right side in ten cases, and on the left side in four cases; in three cases the side was not designated.

The diagnosis of renal adenoma is difficult. A benign tumor is suggested if the mass in the hypochondrium is freely movable with respiration, painless and slow-growing. Roentgen examination may

12. Seng, M. I.: Dilatation of the Ureters and Renal Pelves in Pregnancy: Urological Study, J. Urol. **21**:475, 1929.

13. Kretschmer, H. L., and Doehring, Carl: Adenoma of the Kidney, Surg. Gynec. Obst. **48**:629, 1929.

show the mass. Unless the tumor encroaches on or compresses the renal pelvis, a negative pyelogram may be obtained, especially if the tumor originates from the lower pole. Examination of the urine may not reveal anything abnormal. If there is a sudden onset of gross bleeding, associated with pain in the region of the kidney and a palpable mass, a renal tumor is indicated.

Kretschmer and Randolph [14] reported a case of spindle cell sarcoma in a man, aged 55 years. The patient had not been feeling well for several months and presented himself with epigastric pain occurring after meals, a mass in the left side, swelling in the left testicle and hemorrhoids. General examination revealed a hard, firm mass in the left side of the abdomen. This extended up to the ribs, across the median line, and down to a point just below the left anterior superior spine of the ilium. The tumor moved slightly with respiration. A mass of similar consistence and probably connected with the first mass was palpable just above the umbilicus. A good-sized varicocele was present on the left side. A differential test of function showed only a trace of dye returning from the left side. The pyelogram of the left side showed incomplete filling due to almost complete block of the renal pelvis; only a streak of the bromide appeared. The pyelogram of the right side was negative. A few erythrocytes and pus cells appeared in the urine from each side. A diagnosis was made of malignant tumor of the left kidney.

At operation a large mass, grayish-pink and moderately firm, which was adherent to the surrounding structures was found. The pedicle, which was hard and fibrous, was divided between clamps, and the mass was removed; the wound was closed after ligation of the pedicle. Large masses were noted both above and below the area from which the kidney was removed. These were not removed because of their extent and their proximity to the large vessels. The patient made a good operative recovery but died a year and seven months after operation. Necropsy revealed spindle cell sarcoma of the kidney.

It was pointed out that such a tumor is rare in the adult, but its occurrence in infants is not infrequent. In the reviewed cases in adults all but one of the patients were more than 34 years of age. Hematuria was present in only three cases. Varicocele and hemorrhoids are common accompaniments to malignant renal tumors. Loss of weight was reported in six cases. The preoperative diagnosis of sarcoma of the kidney as distinguished from other types of malignant neoplasms is practically impossible. Eleven cases from the literature were reviewed as to symptoms, and preoperative and operative data.

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14. Kretschmer, H. L., and Randolph, H. S.: Spindle-Celled Sarcoma of the Kidney in Adults, Ann. Surg. **88**:1033, 1928.

[COMPILERS' NOTE.—It is remarkable that, although the components of renal tumors are so varied in cellular characteristics, although there are so many conflicting opinions regarding the classification of such tumors from the standpoint of histogenesis, pure connective-tissue tumors of the sarcomatous type in adults should be encountered so seldom. The case reported by Kretschmer and Randolph is unusual in this respect. Fortunately, the differentiation of sarcoma, hypernephroma, and carcinoma is as yet largely academic. With the advent of newer forms of treatment, however, it will become necessary to attempt differentiation of tissue characteristics.]

Patch [15] reviewed the literature and reported a case of squamous cell carcinoma of the renal pelvis associated with leukoplakia. He stated the belief that his case offered strong evidence in favor of transition between leukoplakia of the upper part of the urinary tract and squamous cell carcinoma of that region. One hundred and twenty-three cases of leukoplakia occurring in the kidneys, ureters and bladder, and 152 cases of squamous cell carcinoma in the kidneys, ureters and bladder were reported. The greater incidence of squamous cell carcinoma is probably because it is so difficult to detect. In thirty-six cases the growth occurred in the kidneys, in six in the ureter and in 110 in the bladder. There were seven vesical cases and three renal cases associated with leukoplakia; in two cases the leukoplakia was in the kidney and the carcinoma was in the bladder. Patch stated the belief that leukoplakia is the predecessor to squamous cell carcinoma and should be considered as a precancerous lesion.

[COMPILERS' NOTE.—Evidence is slowly accumulating that leukoplakia may be the forerunner of squamous cell carcinoma (Hinman and Gibson, Scholl, Kretschmer, von Borza). An analysis of sixty-seven cases of leukoplakia of the renal pelvis which were reviewed revealed the occurrence of seven squamous cell carcinomas and one adenocarcinoma, an incidence of 11.9 per cent (Kutzmann). Six of these occurred in the renal pelvis and two in the bladder. Patch showed that squamous cell carcinoma is only relatively rare in the urinary tract; 152 cases have been reported. There were thirteen cases of leukoplakia and squamous cell carcinoma coexisting in the kidney and bladder, a higher incidence than is surmised by many observers. Significance should be given to Hinman and Gibson's hypothesis that leukoplakia is the forerunner of squamous cell carcinoma. Leukoplakia, although a physiologicometaplastic process, may become a pathologic process in some cases. Its presence alone would tend to maintain an incurable state of chronic inflammation and irritation. The latter maintains con-

15. Patch, F. S.: The Association Between Leukoplakia and Squamous-Cell Carcinoma in the Upper Urinary Tract, New England J. Med. **200**:423, 1929.

tinuous activity of epithelial proliferation as a protective process. Should this proliferative activity and destruction continue for a considerable period, the cells may undergo malignant change. Why a defensive process such as leukoplakia should be stimulated to undergo malignant change is one of the weaknesses of this hypothesis. However, the evidence submitted from time to time is becoming more conclusive. Patch demonstrated the transitional stages on repeated examinations, and although the changes were not definitely malignant, they were undoubtedly precancerous. Hinman, Kutzmann and Gibson were able to demonstrate in one of their cases, although not so definitely, an early papillary downgrowth with a beginning break in the basement membrane, suggestive of a malignant condition and hence considered precancerous. Kretschmer referred to leukoplakia, stone and chronic infection as the recognized predecessors of nonpapillary carcinoma of the renal pelvis. Von Borza, in discussing squamous cell carcinoma, considered constitutional factors, such as the endocrine system. Wolbach, in discussing Patch's report, reviewed some interesting pathologic data in the deficiency diseases or types of avitaminosis. In vitamin deficiency known as xerophthalmia or keratomalacia, extensive distribution of epithelial metaplasia was found in the conjunctiva, the ocular glands, the alimentary canal, the respiratory tract and the genito-urinary tract. It was noted that the epithelium became replaced by stratified keratinizing epithelium, strongly resembling leukoplakia. Wolbach found that a number of the experimental animals with this disease died of obstruction in the genito-urinary tract, caused by its occlusion and desquamated keratinized epithelial cells.]

Bugbee [16] reported a case of leiomyoma of the kidney. His case is unique because of the fact that in the literature he was not able to find the report of a case in which the diagnosis was made during the life of the patient. The patient was a woman, aged 30 years, who had had a lump in the right side of the abdomen for some time. A pyelogram revealed that the kidney was associated with the mass. At operation the kidney and tumor were removed together. The tumor was in the lower pole of the kidney and was enclosed in a thin, fibrous capsule. The diagnosis was leiomyoma of the kidney. The patient recovered.

Creevy [17] observed pyrexia in two cases of malignant nephroma. Israel stated that of 146 operative cases of renal and suprarenal hypernephromas, fever was a symptom in 18.2 per cent; for a considerable

16. Bugbee, H. G.: Leiomyoma of the Kidney: Report of a Case, J. Urol. **21**:363, 1929.

17. Creevy, C. D.: Pyrexia in Malignant Nephroma (Hypernephroma), J. A. M. A. **92**:1256 (April 13) 1929.

period in several instances it had been the only symptom noticed by the patient, who distinguished initial, intercurrent, and final fever, any one of which might be hectic, recurrent or hematuric. From a prognostic standpoint it was difficult to evaluate the fever, since several patients who exhibited pyrexia had remained well for a number of years after operation. On the other hand, it was at times associated with rapid growth or with extension of the tumor beyond the renal capsule, or with the development of metastasis. It also had occurred in cases in which none of these factors was present. Israel concluded that pyrexia was due to the formation in the tumor of specific pyrogenic substances. Creevy stated the belief that malignant nephroma should be considered whenever an obscure fever is present.

[COMPILERS' NOTE.—Fever, in cases of malignant nephroma, is sometimes septic in type, ranging from 105 to 98 F. On some occasions it may remain from 103 to 105 F. for a week at a time. Associated with the fever there may be severe pain along the course of the large nerves, especially the sciatic nerves. With removal of the kidney the temperature usually returns to normal, but in some instances, if there is recurrence of tumor (either local or in distant metastasis) the typical fever and nervous syndrome return. Fever recurring secondarily following operation is almost pathognomonic of metastasis.]

Speciale [18] reported the case of a woman who, for six months, complained of pain in the left loin. Bimanual palpation revealed a soft, smooth, hypertrophied kidney. Urine from the left kidney obtained at cystoscopy contained pus. A diagnosis of pyonephrosis was made.

Examination of the kidney after nephrectomy revealed a malignant tumor. Nearly all of the kidney was composed of soft, grayish, friable tissue with hemorrhagic areas; the whole mass resembled tuberculous tissue. The microscopic aspect was that of perithelioma; many small, round formations, composed of pseudo-epithelial elements were distributed in concentric series around a central zone occupied by capillary blood vessels. Speciale stated the belief that the growth was an endothelioma which had developed from the cellular elements around the capillary blood vessels; proliferation of these cells had given rise to a tumor.

Resection.—Scholl [19] reported a case in which both kidneys were diseased. The patient, a woman, had symptoms of severe urinary infection. Cystoscopy and the roentgen ray revealed much reduction in function and infection in both kidneys with a large stone in the left kidney.

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18. Speciale, F.: Sui periteliomi del rene: Contributo clinico ed anatomopatologico, Riforma med. **44**:848, 1928.

19. Scholl, A. J.: Kidney Resection, Ann. Surg. **88**:1045, 1928.

The left kidney was exposed under gas and oxygen anesthesia, through a posterolateral incision; it was almost twice normal size. The lower pole was rounded, bulbous and edematous, and there were extensive inflammatory perirenal adhesions. After the adhesions were stripped off, the lower segment of the kidney was about 6 cm. wide; it felt hardened, but was readily compressible and somewhat fluctuant. The fatty covering over the pelvis was removed, and an incision 2 cm. long was made in the renal pelvis parallel to the long axis of the kidney; this readily exposed the main segment of the calculus, which was removed through this incision. The middle section of the stone projected through the lower calix, where a smaller, rounded mass completely blocked drainage from the lower part of the pelvis. Since it was not possible to remove the stone in one piece, it was broken and the larger fragment was removed through the incision in the pelvis; the other fragment slipped back into the lower part of the kidney. When the lower end of the calculus slipped away from the calix, thick green pus oozed through the opening, indicating that there was pus under pressure in the lower renal segment and that it was confined there by the ball-valve action of the stone. A transverse incision was made in the parenchyma of the kidney in an area in which apparently normal tissue adjoined the swollen lower segment. The incision opened into the abscess cavity, which contained about 90 cc. of thick, green pus. The wall of the cavity, which comprised the entire lower third of the kidney, was thin and fibrous, and contained little functioning tissue. The lower segment of the kidney, which contained several fragments of stone, was resected. The incision in the kidney was sutured with catgut.

Nine months after operation a divided intravenous phenolsulphonphthalein test revealed normal and equal function in both kidneys. Sixteen months after operation the urine from the bladder was not abnormal, and the patient had gained 16 pounds (7.3 Kg.) and was feeling well.

[COMPILERS' NOTE.—This article, with the deductions to be drawn from its conclusions, is in accord with the more recent trend of thought in conservative renal surgery. If the surgeon can maintain good blood supply and proper drainage to the remaining segment, partial nephrectomy probably will give all that may be desired and often will be the means not only of saving the life of the patient but of restoring him to relatively good health. The maintenance of proper drainage, especially during the first few months after operation, is important. With subsidence of the early inflammatory reaction, the drainage of the kidney will be taken care of by the natural route. The value of persistence with the indwelling catheter and of repeated renal lavage, during the period of healing, cannot be overemphasized, and should be

continued even if, from the clinical standpoint, it seems inevitable that the remaining segment must be sacrificed.

Unquestionably, partial nephrectomy will prove to be a new and fruitful resource to the urologic surgeon in many cases that otherwise would be unsatisfactory surgical risks.]

Stone.—Cifuentes [20] discussed recurrent renal calculi. In an earlier paper he reviewed 359 cases of pelviolithotomy from the literature in which there was recurrence in 3.9 per cent. He divided the infected from the noninfected cases and found that recurrence occurred in only 1.7 per cent of 226 noninfected cases. In the infected cases there was a recurrence of 7.5 per cent. In 9.5 per cent of 941 cases of nephrotomy there was recurrence. Rovsing reported a high percentage of recurrences, fifty-seven in fifty-one cases. He attributed the recurrence to infection with the staphylococcus and *Bacillus proteus.* Gottstein reported on his own cases in which there was 10 per cent recurrence in aseptic cases and 21 per cent in infected cases.

Retention, as well as infection, favors recurrence. Retention may be secondary to ureteral strictures or kinks. The size of the stone apparently has little influence on recurrence, but it has been observed that phosphatic stones are most prone to recur. Cifuentes advised lavage of the renal pelvis after operation as prophylaxis against recurrence.

[COMPILERS' NOTE.—In discussing recurrence in any series of cases of calculi, many factors of importance may be overlooked and the conclusions which are drawn may be misleading. The chemical composition of the stone, the degree and type of infection present, and the persistence of stasis in the urinary tract from which calculi have been removed are features which should be evaluated in each case but are frequently passed over when a large series of cases is studied as a whole.

In general the incidence of recurrence has been greatly decreased since the advent of roentgenograms at the operating table to avoid leaving small stones or fragments. At the present time, this incidence usually should be less than 10 per cent.

Most urologists state the belief that careful and complete operative removal of stones followed by frequent cystoscopic lavage and such surgical measures as will insure good drainage of the urinary tract are the essential factors in clearing up residual infection and avoiding stasis. From a practical standpoint, infection and stasis sum up what is known as the chief causative agents in the formation of stone. Nevertheless, one must not forget that oxalate stones have been produced experimentally in animals by overloading the calcium oxalate

20. Cifuentes, Pedro: Sur la récidive des calculs du rein, J. d'urol. méd. et chir. **26**:289, 1928.

content of the urine, and that such a mechanism may account for recurrent calculi of the oxalate or urate variety, when infection, possibly, is in abeyance.]

Carbuncle.—Lazarus [21] reported two cases of carbuncle of the kidney. The symptoms are usually pain and tenderness in the lumbar region, accompanied by fever and practically negative urinary data. It is frequently preceded by a carbuncle or furuncle elsewhere in the body. Cystoscopic examination is usually negative.

The treatment is early operative intervention. Simple incision and drainage or excision often cure the disease, and nephrectomy should be performed secondarily only if drainage or excision is not successful. In all cases of perinephritic abscess the kidneys should be explored carefully, since many of these are secondary to carbuncle of the kidney. The lesion usually is produced by an organism of attenuated virulence.

Cystic Disease.—Meltzer [22] sent a questionnaire to members of the American Urological Association and compiled reports on 111 cases of polycystic disease of the kidney with surgical symptoms. Nephrectomy was done in fifty-nine cases (53.1 per cent); Rovsing's puncture of cysts was done in thirty-one cases (28 per cent); and decapsulation and puncture were done in five cases. Of the patients treated surgically, four lived forty-eight hours, twenty-four lived from three days to six months, twenty lived from six months to two years, forty-four lived for from two to eight years, three lived nine years, one lived eleven years, one lived twelve years, one lived thirteen years, two lived fourteen years and one lived fifteen years. American urologic experience with this disease reveals that life can be prolonged in 57.6 per cent of the cases for from six months to eight years; in 21.6 per cent, life was maintained from three days to six months after operation.

Clinically, there are apparently no authentic cases of unilateral polycystic disease. If cases supposed to be unilateral in which nephrectomy has been done are traced, evidence of the disease in the supposedly normal and remaining kidney will be found. That unilateral polycystic kidney exists is substantiated by numerous postmortem observations. Preitz found sixteen cases in 1,000 necropsies, and Naumann reported sixteen cases in 10,177 necropsies.

The most commonly accepted explanation of polycystic disease is that it may originate in consequence of embryonic malformations; it is believed also that the condition is both congenital and hereditary.

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21. Lazarus, J. A.: Carbuncle of the Kidney: Report of Two Cases, J Urol. **21**:353, 1929.

22. Meltzer, Maurice: A Contribution to the Surgical Aspects of Polycystic Disease of the Kidney, Brit. J. Urol. **1**:54, 1929.

Osler reported five cases of polycystic disease in five children of one mother. Crawford mentioned numerous cases of this disease in four generations of one family.

Two significant symptoms which require surgical treatment are brisk and recurrent hematuria or abdominal pain. The pain is colicky either when the ureter becomes obstructed by the passage of pieces of blood clot or débris, or when the renal pelvis becomes distended by such occlusions. Dull abdominal pain is due to distention of the renal pelvis, or to pressure on the abdominal viscera by the enlarged renal tumor. Kidd classified the symptoms in three stages: (1) the stage of progressive enlargement of one or both kidneys without other symptoms; this may last for a few months to several years and may be discovered in the course of abdominal palpation; (2) the stage of renal tumor, in which there may not be pain, but a dull ache in the loin, or local pain and tenderness, and (3) the stage of uremia. The greatest aid to diagnosis, besides the symptoms, is the pyelogram which demonstrates the spindle-like outline of the renal pelvis and calices.

Before surgical treatment is considered, a careful general examination should be made, particularly the estimation of the function of the remaining kidney.

[COMPILERS' NOTE.—Although our knowledge of the genesis of polycystic kidney is somewhat obscure, it does seem that the development of this anomaly is in some way related to perverted union of the collecting and secretory parts of the urinary tract. The condition does not manifest itself until somewhat late in adult life, if we assume an anomaly which exists as the result of embryologic maldevelopment. From the number of cases of unilateral disease noted in postmortem studies, it is likewise remarkable that the condition has not at some time been determined clinically on one side only.

As Meltzer emphasized, the best operative effort is the control of bleeding and abdominal pain, which places so many of these unfortunate patients in the invalid class. In spite of both sides being diseased, it is noteworthy that American urologists, according to this report, have employed nephrectomy so frequently (in 53.1 per cent of cases). Although such radical treatment may be indicated to give the patient an interval of freedom from pain or bleeding, provided the major symptoms are on the treated side, the ominous prognosis so far as the ultimate fate of the remaining kidney is concerned would lead to the belief that operative procedures should usually be of a type which would preserve as much of the secreting renal epithelium as possible. One would presume that the operation of puncture of cysts, alone or combined with decapsulation, would be the more frequent procedure, even if the function of the opposite kidney was relatively good.]

Meltzer [23] described a case of echinococcus disease of the kidney in which, at operation, the kidney was found to be a pouch about 30 by 20 cm. in size, filled with echinococcus cysts varying from 1 cm. in diameter to 3 by 5 cm. There were approximately from 800 to 900 cysts; about 200 of these came out crushed and macerated.

Twenty-two cases of echinococcus disease of the kidney have been reported. Two cases were also noted at necropsy. Infection of the kidney with echinococcus is rare, because the larva has to go through the liver, heart and lungs and back to and out of the heart before it is started in the systemic circulation for the kidney. The disease is almost always unilateral. The parasite has been known to survive for twenty years. It may be quiescent for years. Renal or ureteral pain is due to the passage of pieces of the wall of a cyst or pieces of blood clot after the rupture of a cyst, frequently causing intermittent ureteral obstruction. Hematuria may also occur with rupture of a cyst.

A diagnosis can be made only by finding the hooklets in the urine after the rupture of a cyst. Associated with the hooklets are pus cells and erythrocytes depending on the degree of infection. If the process is of long standing, a definite tumor of the kidney may be palpated. Eosinophilia is reported in more than half of the cases.

Nephrectomy is indicated as soon as the diagnosis is made. Of sixteen patients on whom nephrectomy was performed for hydatid disease of the kidney, ten are said to be cured and three improved. Foreign surgeons prefer conservative measures, such as incision and drainage and marsupialization.

Hydronephrosis.—Morison [24] attempted to determine the routes of absorption in hydronephrosis by introducing dyes into the renal pelvis in amounts less than the total pelvic capacity. He observed two routes of absorption, lymphatic and tubular. At the beginning of complete ureteral obstruction there is, for the first two or three days, lymphatic absorption from the walls of the renal pelvis and ureter. Tubular absorption begins after about the third day and continues more actively than lymphatic absorption. A short period of backpressure favors tubular absorption. The convoluted tubules of the peripheral glomeruli are the first to take on this function; as atrophy from pressure progressively supervenes, the subjacent layers continue the progress of reabsorption. In absorbing dye, the cells of the convoluted tubules may demonstrate a slightly altered function. If so, their action would tend to favor the filtration and reabsorption theory of renal secretion.

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23. Meltzer, Maurice: Echinococcus Cysts of the Kidney, J. A. M. A. **92**:1925 (June 8) 1929.

24. Morison, D. M.: Routes of Absorption in Hydronephrosis; Experimentation with Dyes in the Totally Obstructed Ureter, Brit. J. Urol. **1**:30, 1929.

Morison stated the belief that pyelovenous backflow is probably the result of trauma and cannot be regarded as a usual factor in the mechanism of hydronephrosis.

[COMPILERS' NOTE.—The concept of pyelovenous backflow as introduced by Hinman several years ago has been the subject of sharp debate. Morison's experiments and his conclusions obviously place him in the ranks of those opposed to this concept. Whether a relatively open system of communication, physiologic in type, between the venous system and the collecting tubules and pelvis, exists normally is difficult to demonstrate to the satisfaction of all interested in urologic physiology. It is noteworthy that Morison filled the pelves in amounts less than the pelvic capacity. To what degree the pelvis is to be filled in order to initiate pyelovenous absorption without the actual occurrence of traumatic rupture of the venules is the chief point which is to be determined experimentally. Pressure relationships in the renal pelvis in both normal and hydronephrotic states are elusive in actual determination. It will be interesting to note the advance of knowledge along this line within the next few years.]

Perinephritis.—Larru [25] discussed the roentgenologic diagnosis of nonpurulent perinephritis. He noted the disappearance of the outer border of the psoas muscle in its upper part and also the entire or partial disappearance of the inner border of the renal shadow. The two shadows appear to be superimposed on one another. The explanation is that perinephritis, especially inflammation of the psoas muscle, is present, which tends to destroy the outline. It may be found in all renal conditions that tend to cause perirenal adhesions, especially to the psoas muscle, such as calculous pyonephrosis, perinephritic abscess, or renal tuberculosis. Larru found it constantly in renal tuberculosis.

Technic for Removal.—Cathelin [26] divided the types of diseased kidneys which should not be removed into several categories: 1. The adherent pyonephrotic calculous type, especially with adhesions at the level of the hilum, should not be removed because a cleavage plane does not result from the multiple adhesions to surrounding structures. On the other hand, the subcapsular operation exposes only the firm sclerosed hilum, which cannot be accurately ligated. Cathelin stated the belief that the most logical procedure in these cases is simple nephrostomy with digital extraction of the stones. 2. Nephrectomy should not be performed in cases in which a tuberculous kidney is apparently normal. If, during the course of an exploratory operation, the kidney and ureter

25. Larru, E.: Roentgendiagnose der Perinephritis, An. de acad. med.-quirug. espanola **14**:236, 1928.

26. Cathelin: Les reins qu'il ne faut pas enlever, J. d. practiciens, 1929, p. 17.

appear normal, it is better to leave the kidney in place, even if it might necessitate operation later following recurrence or aggravation of the symptoms. 3. A large, adherent carcinomatous kidney should not be removed in young or old patients. In middle-aged patients. nephrectomy is indicated in such cases. 4. Removal of a sclerosed kidney, after an old perinephritic abscess has been opened, would not result satisfactorily and the patient, already weakened, would have to be under anesthesia too long. 5. Nephrectomy should not be done in the presence of a deep atrophied renal mass and extensive sclerolipomatosis.

SUPRARENAL GLANDS

Technic for Removal.—Stultz and Stricker [27] reported a series of cases of epinephrectomy, a surgical procedure which in some instances comes within the province of urology.

They described the following technic: The patient is placed as for left nephrectomy, on a lumbar support which can be raised at will. The right leg is kept flexed, and the left leg is stretched; the plane supporting the lower limbs is inclined, so that the iliocostal space is widened as much as possible. A lateral incision is made from 12 to 15 cm. long, beginning one or two fingerwidths from the outer border of the left rectus abdominus muscle, slightly above or at the level of the umbilicus. It runs toward the upper margin of the twelfth rib, strikes it under an acute angle, crosses the rib, and ends near the external border of the erector spinae muscles. The twelfth rib is resected for a length of from 5 to 8 cm. When the kidney has been identified, the fatty capsule is opened by an incision near the inner border of the upper pole of the kidney and is freed from the perirenal fat. With a large retractor the kidney is pushed downward and forward in the direction of the pubis, so as to facilitate exposure of the subphrenic space. This manipulation also drags down the suprarenal gland, which is still wrapped in its fat, by means of the vascular pedicles that branch from the renal vessels. The gland is then searched for in the epirenal fat, and its base, which faces downward, backward and outward, is usually discovered first. The suprarenal tissue is recognized by its yellow tint and is easily distinguished from fat. The gland is sectioned above a ligature, with the knife directed toward the kidney. A part of the glandular tissue is left behind because of the possibility that the opposite suprarenal gland may be absent or deficient.

In thirteen cases epinephrectomy did not injure the pleura. During operation on a cadaver the pleura was injured because the incision was made too high and too far posteriorly, between the eleventh and twelfth

27. Stultz, E., and Stricker, P.: Technique of Left Epinephrectomy, Surg. Gynec. Obst. **48**:487, 1929.

ribs. The peritoneum is not injured if care is taken to split the fatty capsule of the kidney far behind. The postoperative course is usually normal. The patients have practically no fever, never suffer from shock, and their recovery is rapid.

URETER

Anomalies.—Spitzer and Wallin [28] presented a case in which both kidneys were normal, each containing one normal pelvis and each pelvis leading to the bladder by a ureter which was normally placed. There were also two accessory bodies, one resting above each kidney, which secreted a fluid in no way resembling urine. This fluid was conducted outside the body by tubes which opened at the position of the para-urethral ducts, one on each side of the median line. These tubes followed the course in the walls of the bladder and vagina that is usually taken by Gartner's canal, known to be the persistent remains of the mesonephric duct.

Spitzer and Wallin attempted to classify the so-called ectopic ureters so as to distinguish those that are supernumerary from those that are not.

Infection of Stump.—O'Neil [29] reported a case in which he performed nephrectomy for congenital dilatation of the renal pelvis and the ureter. He removed a portion of the ureter. Cloudy urine later developed. At cystoscopic examination, the stump of the ureter was washed out and a ureterogram showed a sausage-shaped shadow several centimeters long. Dilatation of the orifice of the ureter, proper drainage, and one or two irrigations with silver nitrate effected a complete cure. The author expressed the belief that, in cases of congenital dilatation of the ureter necessitating nephrectomy, complete ureterectomy is indicated.

Wildbolz [30] observed that ureteritis which develops after nephrectomy usually heals spontaneously or after the ureter has been lavaged a few times. As a rule it occurs during the first six months after nephrectomy. He reported a case of a woman, aged 30 years, in whom infection of the ureteral stump occurred unusually late after nephrectomy for nontuberculous pyonephrosis. A year after nephrectomy she went through pregnancy without any complications. Three years after operation, during another pregnancy, she did not feel well and ran a high, continuous fever; the urine became purulent. After normal delivery, the fever continued. Renal tests showed good renal function

28. Spitzer, W. M., and Wallin, I. E.: Supernumerary Ectopic Ureters, Ann. Surg. **88**:1053, 1928.

29. O'Neil, R. F.: Discussion, J. Urol. **21**:119, 1929.

30. Wildbolz, Hans: Discussion, J. Urol. **21**:122, 1929.

in spite of the enormous quantity of pus in the urine. Catheterization of the only kidney revealed clear urine. The pus came from the ureteral stump of the side on which the kidney had been removed. The patient refused surgical intervention. Recovery was complete after treatment by lavage of the ureteral stump.

Stones.—Bumpus [31] reported 1,001 cases in which the diagnosis was stone in the ureter in a clinical study covering a period of nine years. Pain originating in the renal area and radiating toward the bladder was noted in 634 cases (63.4 per cent). Pain in the lower right quadrant without radiation and with little suggestion of renal colic occurred in 138 cases. Removal of the appendix, without relief from symptoms, had been done in thirty-seven of the 138 cases, an incidence of 26.8 per cent. In 226 cases the appendix had been removed.

In 146 cases the stone passed following the manipulation during the first cystoscopic examination, and in 274 other cases manipulation was followed by success in 202 cases. Manipulation was successful in 74 per cent of the cases in which it was attempted, with the exclusion of the 146 cases in which stones passed after a single cystoscopic examination with inclusion of these 146 cases. Manipulation was successful in 85 per cent in which it was attempted.

There were 252 cases of stone in the lower third of the ureter removed surgically and 228 in the upper and middle thirds. In forty-nine cases the urinary obstruction produced by the stone had resulted in such extreme ureteral and renal injury that nephrectomy or nephroureterectomy was required. Except in these forty-nine cases, 60 per cent of all the stones in the lower part of the ureter were removed by manipulation. Reactions occurred thirty-two times (11 per cent) in 274 cases in which manipulation was carried out; two fatal cases were included in this number, in both of which surgical intervention was refused for several days after the suppurative nephritis incident to the manipulation had occurred. Bumpus stated the belief that patients in whom there is marked infection, as well as patients with stones of more than from 1.5 to 2 cm. in diameter that are known to have been present for a considerable period, should be treated by ureterolithotomy rather than by manipulation. Reaction following manipulation can be reduced to the minimum if ureteral catheters are left in the ureter to insure drainage after the stone has been removed. In all the cases in which operation was performed as soon as signs of renal infection appeared, the patients recovered, whereas in the two cases in which it was delayed the patients died. The mortality after catheter manipulation for the entire series was 0.2 per cent.

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31. Bumpus, H. C.: A Clinical Study of Stones in the Ureter, Proc. Staff Meet. Mayo Clinic **4**:140, 1929.

Stricture.—Braasch [32] stated that the only visual evidence of ureteral obstruction is caused by dilatation which persists in repeated ureterograms. That ureteral dilatation occurs early is evident from the dilatation which is always found in the presence of ureteral stones, even if they are small or if they have been present in the ureter only a short time. A factor which may confuse the interpretation of stricture is the dilatation occurring in the ureteral wall as the result of inflammatory changes or atony. The deformity of the ureter may vary from scarcely recognizable irregularity to marked dilatation. Ureteral dilatation as the result of obstruction is usually greater than that which accompanies inflammation. If the dilatation of the ureter results largely from obstruction, it assumes a more uniform outline, particularly if there are single areas of obstruction such as occur in cases of ureteral stone.

Extra-ureteral factors may also be the cause of ureteral obstruction, particularly in the female pelvis, where either inflammatory or malignant tumors which involve the pelvic organs may also involve the ureter. Spasm of the ureteral wall is another probable cause of localized ureteral constriction. Evidence of spasmodic constriction at or near the ureteropelvic juncture, with stone in the renal pelvis, is frequently observed. It usually occurs only in the presence of a single, comparatively small stone, situated in the true renal pelvis, and is probably the result of local irritation. Spasmodic constriction of the ureter is occasionally observed in hypersensitive patients as the result of irritation from the ureteral catheter.

The diagnosis of ureteral stricture by means of the urogram may be difficult. Unless the changes in the wall of the ureter are considerable and definite, it is questionable whether a conclusive diagnosis of ureteral dilatation can be made.

Obstruction.—Hyams [33] stated that obstruction of the lower or pelvic portion of the ureter may be produced by blood vessels which may be normal to the region but pursue an atypical course, or by structures foreign to the area through which they run. The possibility of obstruction should be borne in mind both before and at the time of operation. Treatment is operative in a large percentage of cases. He stated the belief that the subject is of sufficient importance to warrant careful investigation and future anatomic and clinical research.

[COMPILERS' NOTE.—Obstruction in the upper part of the urinary tract produced by aberrant blood vessels is well known and is frequently

32. Braasch, W. F.: Roentgenologic Diagnosis of Ureteral Stricture, Radiology **12**:183, 1929.

33. Hyams, J. A.: Aberrant Blood Vessels as a Factor in Lower Ureteral Obstruction, Surg. Gynec. Obst. **48**:474, 1929.

treated by surgical procedures. Obstruction in the lower part of the tract may be caused by pressure changes at the point of crossing of the vas deferens in the male or of the uterine arteries in the female. However, the occurrence of anomalous blood vessels crossing the pelvic ureter and producing varying degrees of obstruction has not been given much anatomic or clinical consideration. The report of Hyams, especially of his observations at necropsy, is illuminating, and should be the stimulus for much careful investigation along this line. Unquestionably there is reason to assume that a many-branched vessel, like the hypogastric, would be the seat of variations from time to time, as are many-branched vessels in other parts of the body, for example, the renal and hepatic arteries. Hyams seems to have demonstrated definitely that such abnormal branches can compress the ureter in its pelvic portion.]

Marion [34] reported the case of a man, aged 27 years, who gave the following history: At the age of 3 years he had some difficulty in urination. Operation for phimosis did not improve the condition. At the age of 4 he had an attack of hematuria which lasted two days. Since childhood he had had intermittent incontinence, especially at night. At the age of 20, he had had severe hematuria after riding horseback. A large stone was found in the bladder and was removed, but even this did not completely relieve the symptoms. Intravesical cystic dilatation of the left ureter was later found at cystoscopic examination. The urine of the right side was normal; that of the left was thick and purulent. Left nephrectomy was performed and the symptoms disappeared. Apparently the incontinence was not the result of stone, which had existed since childhood, but of infection and distention of the left kidney. Marion stated the belief that this case was somewhat analogous to the occasional occurrence of periods of incontinence in cases of renal tuberculosis.

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34. Marion: Dilatation kystique intravésicale de l'estrémité inférieure de l'uretère et lithiase vésicale infantile infectée; incontinence infantile guérie par disparition de la dilatation kystique, Soc. Française d'urol., Séance de 17 decembre 28, Presse méd. **7**:112, 1929.

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